

1985

# Studies In Synthetic Photochemistry

Rajeev Farwaha

Follow this and additional works at: <https://ir.lib.uwo.ca/digitizedtheses>

---

## Recommended Citation

Farwaha, Rajeev, "Studies In Synthetic Photochemistry" (1985). *Digitized Theses*. 1409.  
<https://ir.lib.uwo.ca/digitizedtheses/1409>

This Dissertation is brought to you for free and open access by the Digitized Special Collections at Scholarship@Western. It has been accepted for inclusion in Digitized Theses by an authorized administrator of Scholarship@Western. For more information, please contact [tadam@uwo.ca](mailto:tadam@uwo.ca), [wlsadmin@uwo.ca](mailto:wlsadmin@uwo.ca).

The author of this thesis has granted The University of Western Ontario a non-exclusive license to reproduce and distribute copies of this thesis to users of Western Libraries. Copyright remains with the author.

Electronic theses and dissertations available in The University of Western Ontario's institutional repository (Scholarship@Western) are solely for the purpose of private study and research. They may not be copied or reproduced, except as permitted by copyright laws, without written authority of the copyright owner. Any commercial use or publication is strictly prohibited.

The original copyright license attesting to these terms and signed by the author of this thesis may be found in the original print version of the thesis, held by Western Libraries.

The thesis approval page signed by the examining committee may also be found in the original print version of the thesis held in Western Libraries.

Please contact Western Libraries for further information:

E-mail: [libadmin@uwo.ca](mailto:libadmin@uwo.ca)

Telephone: (519) 661-2111 Ext. 84796

Web site: <http://www.lib.uwo.ca/>

## CANADIAN THESES ON MICROFICHE

I.S.B.N.

## THESES CANADIENNES SUR MICROFICHE



National Library of Canada  
Collections Development Branch

Canadian Theses on  
Microfiche Service

Ottawa, Canada  
K1A 0N4

Bibliothèque nationale du Canada  
Direction du développement des collections

Service des thèses canadiennes  
sur microfiche

### NOTICE

The quality of this microfiche is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us a poor photocopy.

Previously copyrighted materials (journal articles, published tests, etc.) are not filmed.

Reproduction in full or in part of this film is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30. Please read the authorization forms which accompany this thesis.

THIS DISSERTATION  
HAS BEEN MICROFILMED  
EXACTLY AS RECEIVED

### AVIS

La qualité de cette microfiche dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de mauvaise qualité.

Les documents qui font déjà l'objet d'un droit d'auteur (articles de revue, examens publiés, etc.) ne sont pas microfilmés.

La reproduction, même partielle, de ce microfilm est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30. Veuillez prendre connaissance des formules d'autorisation qui accompagnent cette thèse.

LA THÈSE A ÉTÉ  
MICROFILMÉE TELLE QUE  
NOUS L'AVONS REÇUE

STUDIES IN SYNTHETIC PHOTOCHEMISTRY

by

Rajeev Farwaha

Department of Chemistry

submitted in partial fulfillment  
of the requirement for the degree of  
Doctor of Philosophy

Faculty of Graduate Studies  
The University of Western Ontario  
London, Ontario  
November, 1984

© Rajeev Farwaha 1984.

## ABSTRACT

### PART A

The photocycloadditions of alkenes or allene to steroidal enones has been shown to occur in the adsorbed state. This reaction normally occurring from the (less hindered)  $\alpha$  side has been found to be directed towards the (more hindered)  $\beta$  side by adsorption of the steroidal enone on dry silica gel and alumina surface. The adsorption of the enone on silica gel also, apparently, disfavors the conformational inversion in the intermediate 1,4 biradical, required for the formation of trans-fused products. The changes in composition of the products are frequently such as to be synthetically useful, and in some cases, e.g. the addition of allene to epi-testosterone (15c) and testosterone propionate (15a) on alumina, lead to complete reversal of stereochemistry to that observed in the methanolic solution.  $^{13}\text{Cmr}$  and x-ray diffraction analysis have been used to establish the structure of a 1,3 allene photocycloadduct with  $3\beta$ -acetoxy- $\Delta^{8,9}$ -cholesten-7-one; a mechanism of formation has been proposed involving a triplet carbene. For a series of cyclic enone-allene photocycloaddition it is shown that normally favored formation of the  $\beta\gamma$ -regioisomeric adduct in homogeneous systems can be shifted to favor the  $\gamma\delta$  adduct on a silica gel surface. The formation of the  $\gamma\delta$  adduct is explained by assuming that the initial bond formation occurs at the  $\text{C}_\alpha$  of enone.

## PART B

A photochemical approach to illudinine involving the "de Mayo" reaction namely, photocycloaddition of enolized heterocyclic 1,2-dione (23) to 3,3-dimethyl cyclopentene has been proposed. A strategy for the synthesis of 5,6-dihydro-2-pyridin-7-one (25) involving regioselective metalation of pyridine, intramolecular acylation of enamine and homolytic acylation of pyridine has been attempted. The synthesis of  $\gamma$ -homocinchomeric acid dimethyl ester (38), a precursor to the enone (23) involving regiospecific nucleophilic addition to 3-pyridyl- $\Delta^2$ -oxazoline has been carried out; a mechanism of formation, involving a lactam, has been proposed. Alternatively (38) is synthesized involving Arndt-Eistert rearrangement of  $\beta$ -diazoacetyl nicotinate (50).

## ACKNOWLEDGEMENTS

The author wishes to thank Professor Paul de Mayo for his guidance, helpful advice and encouragement during the course of this work.

Thanks also to Professor A.C. Weedon for his advice and help, particularly with respect to the synthesis of illudinine. Dr. Vinod Dave with whose help the work described in Chapter 3 was accomplished is gratefully acknowledged. Dr. Y.C. Toong with whom I had the pleasure to work with for a short while and whose expertise and knowledge I benefitted from also deserves recognition. I would also like to thank fellow graduate students and postdoctoral fellows in de Mayo's research group for their help throughout the entire course of the study.

Finally, I am very thankful to my wife, Dalbir, for her encouragement and help at every step of the way.

# TABLE OF CONTENTS

	Page
CERTIFICATION OF EXAMINATION.....	ii
ABSTRACT.....	iii
ACKNOWLEDGEMENTS.....	v
TABLE OF CONTENTS.....	vi
LIST OF TABLES.....	x
LIST OF FIGURES .....	xi
 Part A: Steric Modification of Enone Photocycloaddition by Adsorption on Silica Gel and Alumina	 1
 Chapter 1 - GENERAL INTRODUCTION	
1.1 Structure of porous silica.....	2
1.2 Adsorption of organic molecules on silica surface	7
1.3 Surface groups on $\gamma$ -alumina.....	11
1.4 Absorption spectra of adsorbed molecules.....	11
1.5 Photochemistry of adsorbed radicals.....	13
1.6 Unimolecular reactions of adsorbed molecules...	21
1.7 Bimolecular reactions of adsorbed molecules....	24
1.8 Scope of the present investigation.....	25
 Chapter 2 - ENONE PHOTOCYCLOADDITION BY ADSORBED MOLECULES ON SILICA GEL AND ALUMINA	
2.1 The reaction mechanism.....	27
2.2 Electronic nature of enone triplet.....	30
2.3 Stereochemical considerations.....	31
2.4 Choice of substrates.....	35
RESULTS AND DISCUSSION	
2.5 Photocycloaddition of testosterone propionate (15a) to ethylene.....	37
2.6 Photocycloaddition of testosterone propionate (15a) to cyclopentene.....	42
2.7 Photocycloaddition of testosterone propionate (15a) to allene.....	47
2.8 Photocycloaddition of testosterone and <u>epi</u> - testosterone to allene.....	53
2.9 Photocycloaddition of 12-methoxy-18-19-bisnorpodocar- pa-4,8,11,13-tetren-3-one (24) to allene.....	54
2.10 Photocycloaddition of $\Delta^{4,6}$ -androstadien-3-one-17 $\beta$ - ol-propionate (26) to cyclopentene.....	56
2.11 Photocycloaddition of 17 $\beta$ -acetoxy-5 $\alpha$ -androst-1-en- 3-one (30b) to cyclopentene.....	58
2.12 Photocycloaddition of 3 $\beta$ -acetoxypregna-5,16-dien- 20-one (31a) and 3 $\beta$ -hydroxypregna-5,16-dien-20- one (31b) to ethylene.....	58
2.13 Conclusion.....	60
 Chapter 3. MORE ON THE STEREOCHEMISTRY OF ENONE PHOTOCYCLOADDITION	
3.1 INTRODUCTION	
3.1.1 Wiesner's Proposal.....	62



3.1.2	Evidence for initial bond formation at $\alpha$ -carbon and $\beta$ -carbon of enones.....	63
3.1.3	Exceptions to the Wiesner's rule in homogeneous systems.....	65
3.1.4	Exceptions to Wiesner's proposal in heterogeneous systems.....	67
3.1.5	Choice of substrates.....	68
3.1	RESULTS AND DISCUSSION	
3.2	Photocycloaddition of 3 $\beta$ -acetoxy- $\Delta^{8,9}$ -cholesten-7-one (48a) and allene on silica.....	70
3.3	Structural determination of the reported photocycloadducts.....	71
3.4	Structural determination of the new photoadducts	72
3.5	Mechanism for the formation of $\gamma\delta$ -unsaturated adduct.....	79
3.6	Photocycloaddition of 3 $\beta$ -acetoxy- $\Delta^{8,9}$ -cholesten-11-one (48b) to allene.....	80
3.7	Formation of head-to-tail photoadducts on silica gel.....	81
3.8	Photocycloaddition of allene to isophorone (56).	86
3.9	Photocycloaddition of allene to enones (34,56,58, 60,62 and 64).....	87
3.10	Photocycloaddition of bicyclo[4.4.0]-dec-1(6)-en-one (58) to allene.....	88

#### Chapter 4 - EXPERIMENTAL - PART A

4a.1	General	
4a.1.1	Spectra.....	91
4a.1.2	Melting points.....	91
4a.1.3	Gas chromatography.....	91
4a.1.4	High Pressure Liquid Chromatography...	91
4a.2	Materials	
4a.2.1	Solvents.....	92
4a.2.2	Adsorbents.....	92
4a.2.3	Gases.....	92
4a.2.4	Commercially available enones.....	92
4a.2.5	Enones Synthesized.....	92
4a.3	Procedure for Silica gel and Alumina experiments	
4a.3.1	Procedure for sample preparation and irradiation on silica gel.....	94
4a.3.2	Quantitative product analysis.....	97
4a.3.3	Procedure for sample preparation and irradiation on alumina.....	97
4a.3.4	Irradiation on silica gel.....	97
4a.3.5	Solution irradiations.....	98
4a.5	Preparations of steroidal enone photoadducts..	98
	PART B	
4b.1	GENERAL	
4b.1.1	NMR Spectra.....	108
4b.1.2	Compounds used.....	108
4b.1.3	Procedure for sample preparation and irradiation on dry silica.....	108
4b.1.4	Solution irradiation.....	109
4b.1.5	Sample analysis.....	109

4b.2 Adduct Products.....	109
REFERENCES.....	117
Part B: Towards the Total Synthesis of Illudinine..	125
Chapter 5 - AN APPROACH TO THE SYNTHESIS OF ILLUDININE	
INTRODUCTION	
5.1 Isolation and occurrence.....	126
5.2 Classification.....	126
5.3 Biosynthesis of Illudinine.....	129
5.4 Structural Studies.....	129
5.5 Woodward's total synthesis of illudinine, 1a...	131
5.6 Wenkert's total synthesis of Methyl-demethyl- illudinate, 20.....	133
5.7 Fungal metabolites as targets in Organic Synthesis	133
5.8 The de Mayo Reaction.....	133
5.8.1 Acyclic 1,3 diketone.....	135
5.8.2 Cyclic 1,3 diketone.....	135
5.8.3 Intramolecular Additions.....	136
5.8.4 Cyclic 1,2 diones.....	136
5.8.5 Photochemical approach to Illudinine, 1a	138
Results and Discussion	
5.9 An approach to the synthesis of 5,6-dihydro-2- pyridin-7-one, 25 via regioselective metalation of pyridine.....	138
5.9.1 Synthesis of methyl( $\beta$ -4-pyridyl) propionate, 29b.....	139
5.9.2 Attempted synthesis of 5,6-dihydro-2- pyridin-7-one, 25.....	141
5.9.3 Identification of 30.....	142
5.10 Attempted synthesis of 25 by an intramolecular acylation of enamine.....	145
5.10.1 Synthesis of N-benzyl pyridinium methyl propionate.....	145
5.10.2 Reduction of the pyridinium salt, 31a..	146
5.10.3 Attempted cyclization of dihydropyridine esters.....	146
5.11 Strategy for the synthesis of 25 based on the homolytic acylation of pyridine.....	147
5.11.1 Synthesis of 4-Pyridyl-propionaldehyde.	148
5.11.2 Attempted cyclization of 4-pyridyl- propionaldehyde.....	149
5.12 Synthetic approach to indanone derivative 37 via acyloin condensation of 38.....	150
5.13 Synthesis of $\gamma$ -homocinchomeric acid dimethyl ester 38.....	151
5.13.1 Heteroatom facilitated lithiation of pyridines.....	151
5.14 Approach to the synthesis of $\gamma$ -homocinchomeric acid dimethyl ester, 38 via regiospecific metalation of 3-pyridyl-oxazoline.....	153
5.14.1 Synthesis of 2-(3-Pyridyl)-4,4-dimethyl- $\Delta^2$ -oxazoline, 39a.....	153

5.15 Alkylation of 4-lithio derivative.....	154
5.16 Approach to the synthesis of 38 via addition of oxazoline stabilized carbanion to Michael acceptor.....	156
5.17 Regiospecific nucleophilic addition to pyridine	157
5.18 Synthetic approach via regiospecific addition of a monoanion of ester to pyridyl oxazoline.....	159
5.19 Synthetic approach via addition of dianion of acetic acid to 3-pyridyl oxazoline.....	159
5.19.1 Identification of 45.....	161
5.20 Synthetic approach via addition of monoanion of nitrile to 3-pyridyl oxazoline.....	162
5.20.1 Attempted acidic hydrolysis of 4-picolyl nitrile derivative.....	163
5.21 Basic hydrolysis of 4-picolyl nitrile derivative	164
5.22 Synthesis and hydrolysis of cinchomeric dimethyl ester, 48b.....	168
5.23 Synthesis of $\beta$ -diazoacetyl nicotinate, 50.....	169
5.24 Arndt-Eistert rearrangement of 50.....	170
5.25 Attempted acyloin condensation of <u>iso</u> - nicotinic ester.....	170
5.26 Attempted acyloin condensation of homophthalic dimethyl ester.....	171
5.26.1 Synthesis of homophthalic dimethyl ester, 54.....	172
5.26.2 Attempted cyclization and identification of 56.....	172
5.27 Attempted acyloin condensation of $\gamma$ -homocinchomeric acid dimethyl ester.....	173
5.28 Synthesis of gem-dimethyl cyclopentene.....	174
Chapter 6 - EXPERIMENTAL	
6.1 General	
6.1.1 Spectra.....	177
6.1.2 Melting Points.....	177
6.1.3 Chromatography.....	177
6.1.4 Aqueous Work-up.....	177
REFERENCES.....	201
VITA.....	205

# LIST OF TABLES

TABLE	DESCRIPTION	PAGE
2.1	Conditions and the results of the cycloaddition of enones to alkenes or allene	40
2.2	Circular dichroism of stereoisomeric 3-keto-4-ene-steroid adducts	49
3.1	Conditions and the results of the cycloaddition of enones to allene	84
3.2	<sup>13</sup> C shielding data for adducts X-Y	85

## LIST OF FIGURES

Figure	Description	Page
1	Surface structures of silica gel: a) isolated hydroxyls; b) vicinal hydrogen-bonded hydroxyls; c) geminal hydroxyls; d) hydrated hydroxyls.	3
2	Bonding on the silica gel surface	5
3	Surface arrangements of hydroxyls on alumina, type 1: hydroxyl coordinated to a single $Al^{+3}$ ; type 2: hydroxyl coordinated to two $Al^{+3}$ ; type 3: hydroxyl coordinated to three $Al^{+3}$ .	9
3.1	A view of 53c showing the molecular configuration.	73
4.1	Apparatus for preparation of dry silica gel and alumina samples.	95

**Part A: Steric Modification of Enone Photocycloaddition  
by Adsorption on Silica Gel and Alumina.**

## CHAPTER 1

### GENERAL INTRODUCTION

#### 1.1 STRUCTURE OF POROUS SILICA

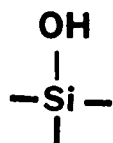
Silica, like carbon, has several polymorphs. Apart from the amorphous state, it is known to exist in numerous crystalline modifications. The most important forms are quartz, tridymite, and cristobalite. In silica, each silicon atom is surrounded tetrahedrally by four oxygen atoms. The bonding is intermediate in type between covalent and ionic.<sup>1</sup> There is some  $d\pi-p\pi$  bonding between silicon and oxygen.

Porous silica, more commonly referred to as silica gel, is one of the many forms of amorphous silica. Amorphous silica is formed by polycondensation of polysilicic acid. Colloidal silica is a network of interlinked  $\text{SiO}_4$  tetrahedra with the residual valences on the surface occupied by hydroxyl groups.

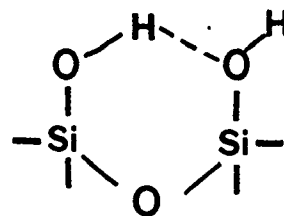
The surface of silica gel is characterised by the presence of terminal silanol functions (isolated, geminal, vicinal) and of siloxane bridges, usually with accompanying physisorbed water molecules (see figure 1).<sup>2</sup> Physico-chemical and infrared studies,<sup>3</sup> and more recently nmr studies,<sup>4</sup> have led to an acceptable, if incomplete, picture.

The activity of silica gel depends strongly upon the amount of physisorbed water present on the surface.

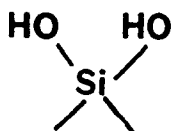
- Measurements performed by Fripiat et al<sup>5</sup> indicate that the amount of physisorbed water decreases with increasing



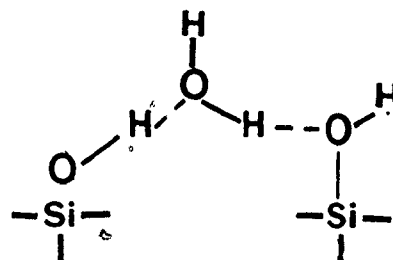
a



b



c



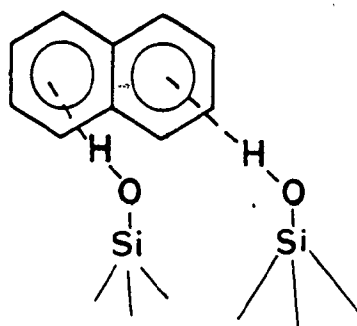
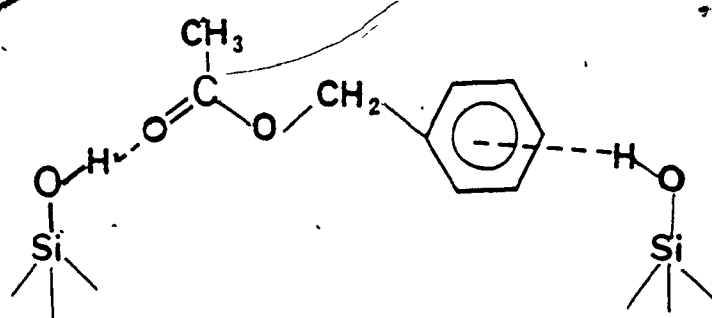
d

Figure 1. Surface structures of silica gel:  
 a) isolated hydroxyls; b) vicinal hydrogen-bonded hydroxyls; c) geminal hydroxyls; d) hydrated hydroxyls.



temperature, and for temperatures higher than 230°C it is reduced to zero. The number of surface silanol groups per unit surface area has been determined by various physical and chemical methods. The results of all methods coincide well and lead to an average value of  $\sim 6 \text{ SiOH}/100 \text{ \AA}^2$  for an equilibrated surface.<sup>6</sup> The number of hydroxyl groups on silica gel surface depends on the treatment of the silica sample. Heating silica gel above 250°C results in dehydroxylation of silanol groups to form strained siloxane bonds. The dehydration of silanol groups is reversible and rehydroxylation of the siloxane bonds takes place instantaneously if the dehydration is carried below 450°C. At 500-600°C only the free silanol groups survive, an estimated  $\sim 2 \text{ SiOH}/100 \text{ \AA}^2$  remain at 500°C. If the heating is taken to 800°C  $\sim 1.7 \text{ OH}/100 \text{ \AA}^2$  remains on the surface. These groups may either be isolated or geminal. Hair et al<sup>7</sup> showed that 60% of the  $\sim 1.7 \text{ OH}/100 \text{ \AA}^2$  retained after heat treatment at 800°C are single silanol groups and the remaining 40% are geminal. Complete dehydroxylation of the silanol groups on silica occurs when it is heated from 900-1000°C. For the highly dehydroxylated silica gel containing few residual silanols, rehydration is quite slow. Since the siloxane bonds formed in dehydration are known to be hydrophobic they probably serve as poor sites for attack of water on the siloxane linkage. The difference in physical and chemical behaviour, depending upon the pretreatment of silica gel, has been attributed to

Figure 2. Bonding on the silica gel surface.



the presence of 'strained' siloxane bonds in silica heated to no more than 450°C. Boehm pointed out that the strain is relieved by annealing on further heating.<sup>8</sup> [Siloxane bonds are opened readily with strong bases. Nucleophilic attack on the silicon atom is involved in the reaction mechanism.] Fripiat's findings<sup>5</sup> have been recently supported by nmr studies<sup>4</sup> in which, additionally, the proportion of geminal-hydroxyl sites to single hydroxyl sites, previously the subject of much debate, was determined.

The surface area of silica gel is usually determined by the BET (Brunauer, Emmett and Teller) nitrogen adsorption method. The value obtained for surface area is dependent upon the cross sectional area of the molecule used to cover the surface with a monolayer.<sup>9,10</sup> Large molecules cannot follow the fine details of an irregular surface and consequently smaller surface values are obtained.<sup>11</sup> }

## 1.2 ADSORPTION OF ORGANIC MOLECULES ON SILICA SURFACES

The principal sites responsible for the adsorption of organic molecules on silica gel consist of surface silanol groups and the forces responsible for the adsorption of organic molecules are: 1) electrostatic interactions<sup>12</sup>; 2) London-type dispersion forces arising from induced dipole interactions<sup>13</sup> and 3) hydrogen bonding.<sup>6</sup> The binding of organic molecules containing  $\pi$  bonds or lone pairs is largely by hydrogen bonding to the silanols or to the

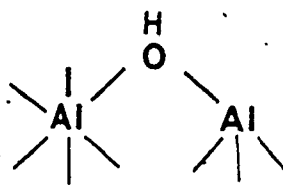
physisorbed water (see Fig. 2). The hydrogen bonding interactions are interpreted by the change in the stretching frequency of the (Si-OH) bond and the extent of the shift indicates the degree of interaction between silanols and an adsorbed molecule. These interactions are not governed by the total dipole moment of the polar molecules but rather by the local distribution of electrons (such as  $\pi$  electrons) at the periphery of the given adsorbate molecule.<sup>6</sup> The magnitude of hydrogen bonding to a  $\pi$  system is -9 kJ/mol as compared to -40 kJ/mol for the heteroatom.<sup>12</sup> The lone pair of electrons on oxygen in furan is distributed through conjugation throughout the ring and silanol groups form  $\pi$  complex with the aromatic ring of furan. A frequency shift of  $120\text{ cm}^{-1}$  is observed. On the contrary, a large frequency shift ( $470\text{ cm}^{-1}$ ) is observed for tetrahydrofuran in which the oxygen lone pairs interact with the silanol group.<sup>5</sup>

The size of most organic molecules is large compared to the spacing between adjacent silanol groups and they can interact with more than one silanol group.<sup>6</sup> The degree of interaction also depends upon the heat treatment of silica gel and polarity of the substrate. The strongest adsorption of organic molecules occurs with thermally dehydrated silica gel having only isolated silanol groups. On the other hand, the fully hydroxylated silica surface is better in providing multiple adsorption sites for polyunsaturated hydrocarbons that can 'fit' the adsorbate.<sup>8</sup>

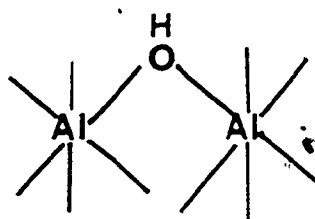
Figure 3. Surface arrangement of hydroxyls on alumina,  
type 1: hydroxyl coordinated to a single  $\text{Al}^{+3}$ ; type 2:  
hydroxyl coordinated to two  $\text{Al}^{+3}$ ; type 3: hydroxyl  
coordinated to three  $\text{Al}^{+3}$ .



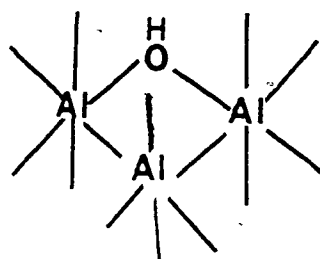
Type 1



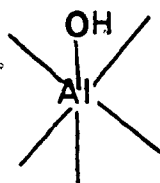
Type 2



Type 2



Type 3



Type 1

### 1.3 SURFACE GROUPS ON $\gamma$ -ALUMINA

The metal oxygen bond of alumina is more ionic in character than that of silica. The hydrogen donor and acceptor properties of  $\text{Al}_2\text{O}_3$  are, therefore, different from those of silica.

Five different types of hydroxyl groups have been reported on alumina surface: 1) terminal (OH) groups coordinated to a single  $\text{Al}^{+3}$  in a tetrahedral position or coordinated to a single cation in an octahedral interstice; 2) bridging (OH) groups linked to two cations in the octahedral positions or linked to two cations in octahedral and tetrahedral position respectively; 3) (OH) coordinated to three  $\text{Al}^{+3}$  in an octahedral position. All these possible arrangements are shown in (Fig. 3).<sup>14</sup> These environmental differences lead to different acidic and hydrogen bonding properties of various (OH) groups. Peri<sup>15</sup> observed three resolved hydroxyl stretching bands, at 3698, 3737, 3795  $\text{cm}^{-1}$ , after degassing the surface at 650°C; these bands were assigned to isolated noninteracting (OH) groups. The isolated (OH) groups are progressively removed from the surface at increasing degassing temperatures and it leaves the coordination sphere of  $\text{Al}^{+3}$  incomplete. Such  $\text{Al}^{+3}$  acts as a powerful electron acceptor.

### 1.4 ABSORPTION SPECTRA OF ADSORBED MOLECULES<sup>13</sup>

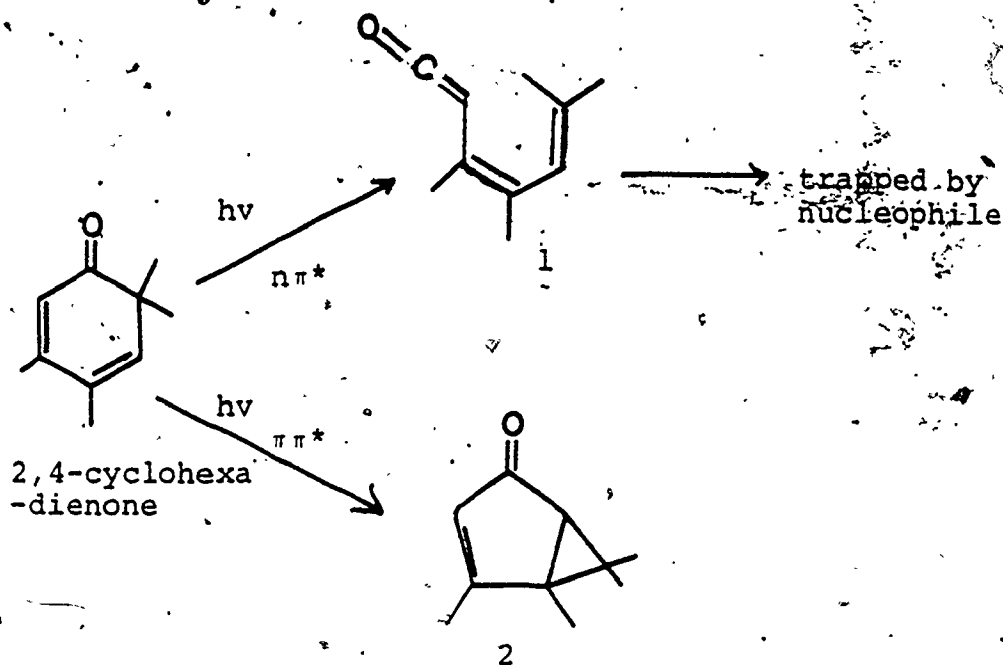
Most of the absorption spectra of adsorbed molecules have been recorded by immersing the adsorbent in the



organic solvent of the same refractive index, in order to increase the transparency. In general, red spectral shifts occur with adsorption of compound on the silica gel if the excited state of the molecule experiences an increase in permanent dipole or if it is more polarizable than the ground state; blue shifts occur if the reverse is true. The magnitude of the spectral shift observed is a direct measure of the adsorbate-adsorbent interactions. Recently, photoacoustic spectroscopy<sup>16</sup> has been used to study the photoisomerization of thioindigo adsorbed on alumina. The absorption spectra of opaque materials has been recorded by reflectance spectroscopy.<sup>17</sup>

The adsorption of benzene, naphthalene and anthracene caused a small spectral shift indicating a weak interaction with silica. Leermakers observed a red shift of 40 nm in all-trans-retinal adsorbed on a silica gel-solvent slurry. A large blue shift was observed in the charge transfer band of ethyl-4-carbomethoxypyridinium iodide and from it a Kosower polarity parameter of Z-88 was obtained for silica (between water and methanol).<sup>18</sup>

In the absorption spectra of 2,4-cyclohexadienone the  $n\pi^*$  band is the lowest singlet state. On adsorption of 2,4-cyclohexadienone on silica, this  $n\pi^*$  band is obscured by the  $\pi\pi^*$  band.<sup>19</sup> Such inversion of excited states has chemical consequences.

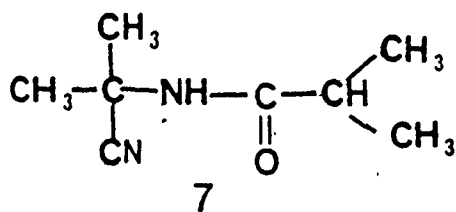
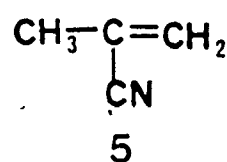
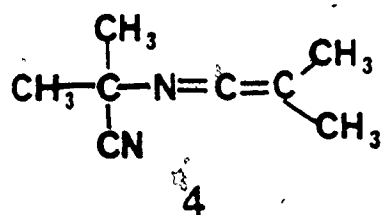
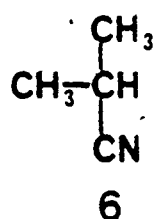
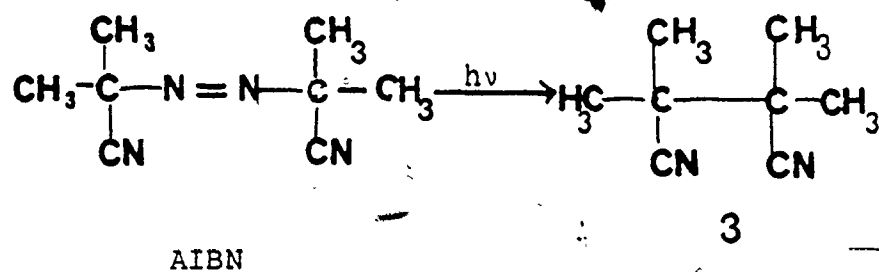


The ketene 1 is obtained by the photolysis of 2,4-cyclohexadienone in non polar solvents, whereas the bicyclic ketone 2 is the only product in polar medium (silica gel-solvent).

Dibenzotropone (DBT), adsorbed on dry silica, exhibited a very large red shift in the absorption spectrum. The red shift observed was a direct function of the heat treatment of silica gel.<sup>20</sup>

### 1.5 PHOTOCHEMISTRY OF ADSORBED RADICALS

In the earlier experiments, the silica gel (adsorbent) - organic solvent slurries were used. This system is complicated by the fact that some reaction also may occur from the molecules in the liquid phase. Special attention has been devoted by de Mayo in his recent studies on the question of translational movement of adsorbed radicals on dry silica gel (as distinct from slurries) during



Scheme I

photochemical reactions.

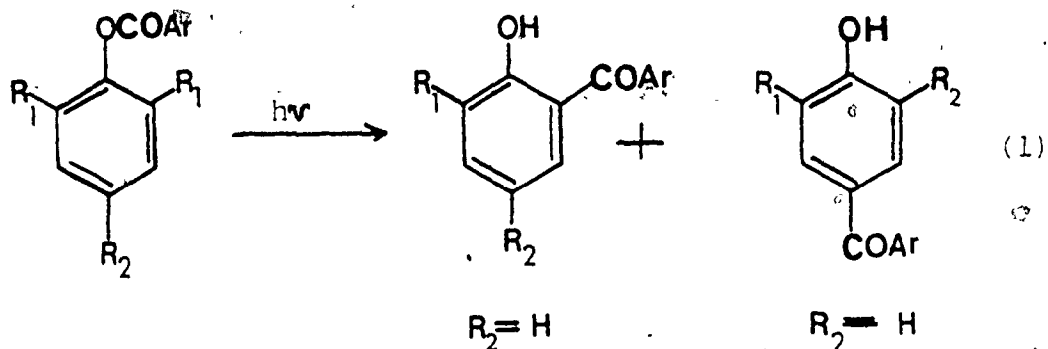
The direct irradiation of AIBN in benzene gave product distribution (3 55%, 4 40%, 5 and 6 5% each) (Scheme I).<sup>21</sup> Leermakers reported that photolysis of AIBN in silica-benzene slurry led to the formation of symmetrical coupling product 3 in -90% yield.<sup>22</sup> It was claimed, in explanation, that the cyanopropyl radicals were anchored to the surface active sites thus restricting their rotational movements and consequently did not produce the unsymmetrical coupling product 4. de Mayo and Coworkers<sup>23</sup> have recently published a revised version of the above proposal by Leermakers. Irradiation of AIBN in silica gel-benzene slurry and on dry silica gave substantial amount of unsymmetrical coupling product, ketenimine 4, together with its hydrolysis product, amide 7. This clearly demonstrated that both rotational and translational movements of cyanopropyl radicals could occur on a silica gel surface. Deuterium labelling experiments with AIBN indicated that there was predominately geminate recombination of singlet cyanopropyl radical pairs while the non-geminate recombination product was obtained from triplet radical pairs.

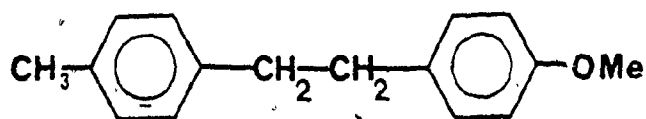
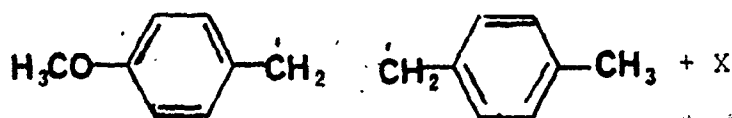
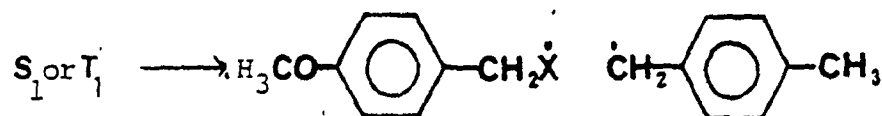
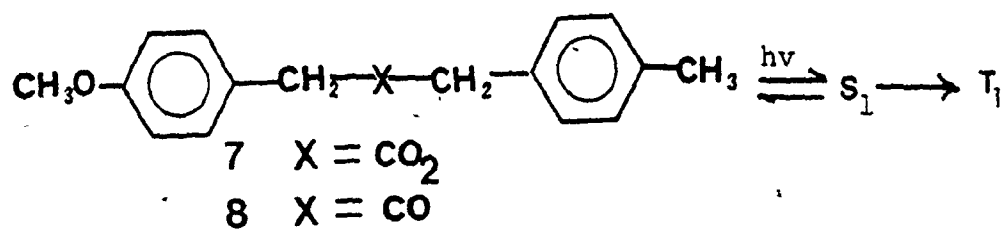
Leermakers showed that the quantum yield for photodecomposition of tetramethyl-1,3-cyclobutanedione (TMCD) in solution was reduced three fold by adsorption on to silica gel. TMCD is known to undergo a two step rupture for release of carbon monoxide. It was claimed, in

explanation, that the radicals formed in the initial step were held in close proximity on the surface, so that bond reformation competed effectively with irreversible photodecarbonylation,<sup>24</sup>

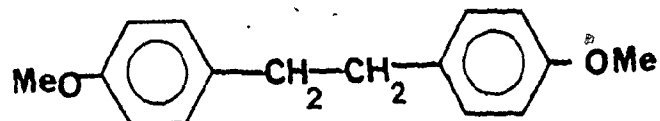
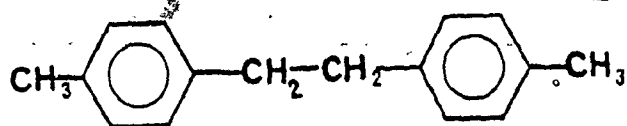
The Photo-Fries rearrangement of aromatic esters was examined on dry silica gel and silica gel-pentane slurries (1).<sup>25</sup> The reaction in solution involves homolysis in the singlet excited state, followed by recombination, in the solvent cage, of radical pairs. A better yield of products was obtained with ortho-substituted aromatic esters on a silica surface. It was claimed, in explanation, that a surface quasi cage effect was operative which resulted in slow diffusional separation of radical pairs in contrast to that in solution.

#### Photo-Fries rearrangement





Unsymmetrical product

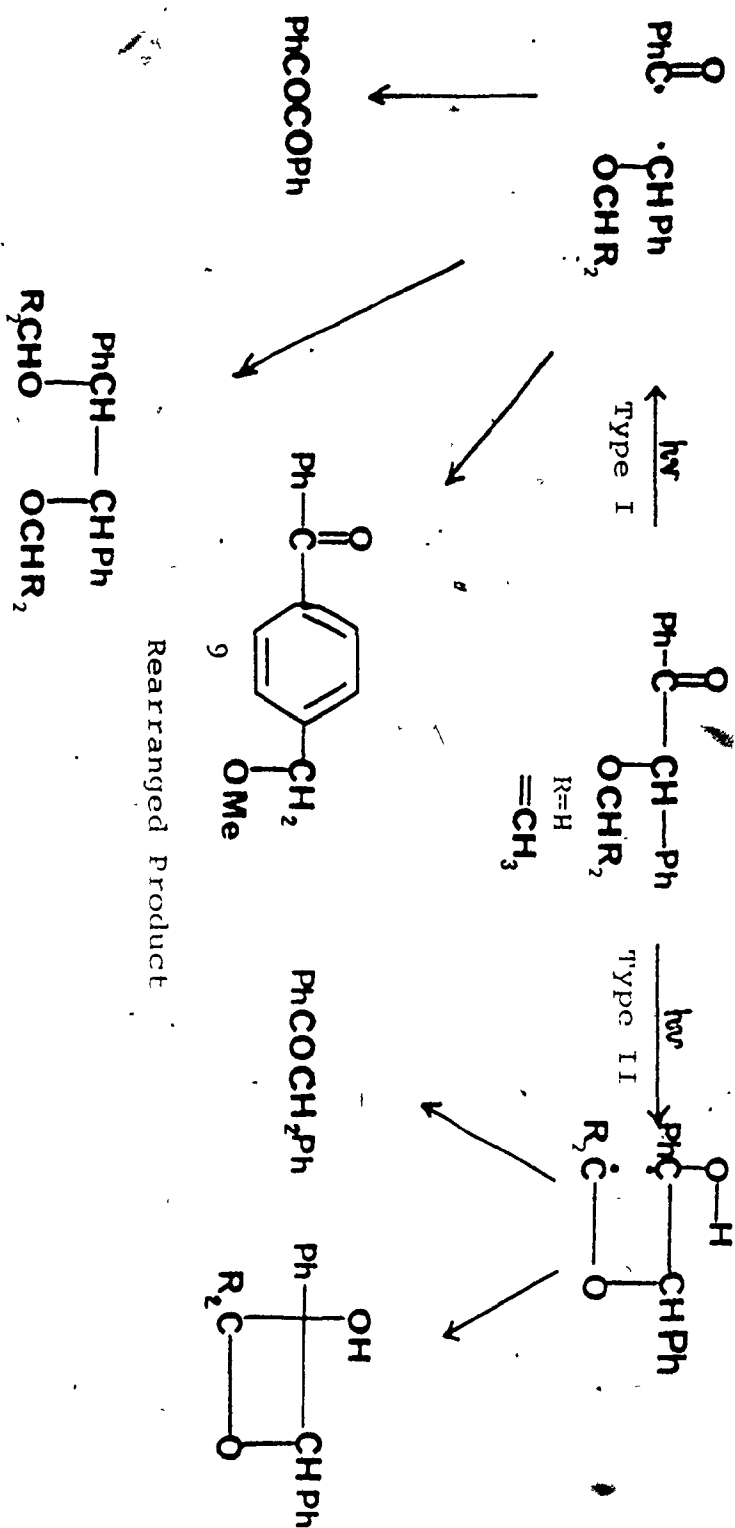


symmetrical products

Scheme II

In continuation of studies on adsorbed radical pairs, de Mayo and coworkers carried out the photolysis of benzyl phenylacetate 7 and a dibenzylketone 8 (Scheme II).<sup>26</sup> The surface mobility of adsorbed radicals was determined by the amount of nongeminate recombination of the original radical pairs. The decomposition of dibenzyl ketone 8 in solution has been established as being via the triplet pathway and that of the ester is believed to follow a singlet pathway. A greater geminate radical pair recombination was observed in the ester than in the ketone, at room temperature which was attributed to the difference in the spin multiplicity. At low temperature, the "cage" properties of silica gel became important and an increase in geminate radical pair recombination was observed.

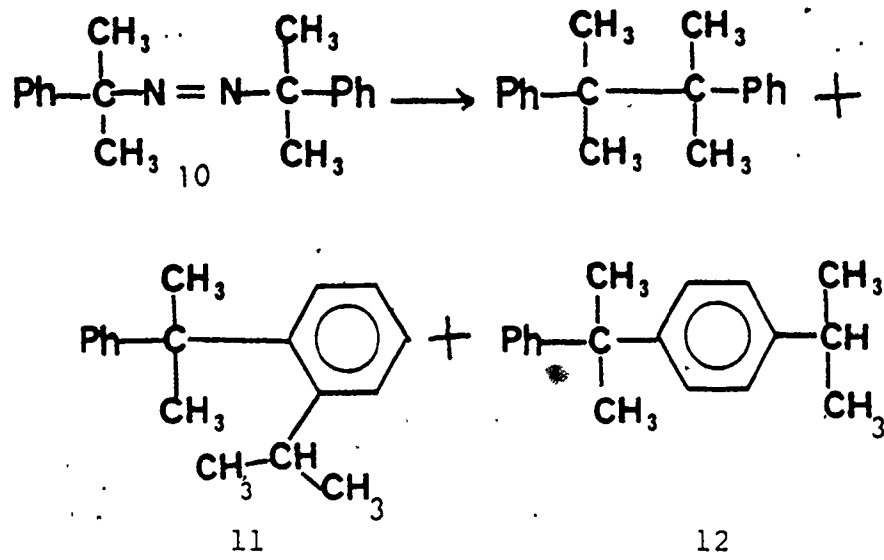
de Mayo and coworkers have recently reported a deviation in the course of reaction in benzoin methyl ether and benzoin isopropyl ether by adsorption on silica gel surface (Scheme III)<sup>27</sup>. The products from benzoin isopropyl ether photolysis on silica gel at  $-80^{\circ}\text{C}$  were 70% Type I, of which 60% was rearranged product, 9, and 25% Type II. In contrast, in methanol at  $-80^{\circ}\text{C}$  only 20% rearranged product 9 and no Type II products were observed. The increased formation of the rearranged product 9 at low temperature on dry silica gel was attributed to the suppression of translational motion of radical pairs generated. The increase in Type II process over Type I was attributed to the conformational



Scheme III



restrictions imposed on the benzoin ether by the surface.



Scheme IV

Leffler reported<sup>28</sup> the decomposition of azocumene 10 on a silica gel surface pretreated at 850°C, to give rearranged dimers in 2-6% yield (Scheme IV). The formation of head-tail dimers (11 and 12) was explained by the preferential attachment of cumyl radical on the surface active sites, which catalyzed the rearomatization of the quinoidal dimers. The above conclusion differs from that drawn by de Mayo in a study of photolysis of dibenzyl ketone on silica gel.<sup>26</sup> A similar product distribution was observed at low and high coverages during the photolysis of dibenzylketone on dry silica gel which clearly indicated that in this case all the adsorption sites were equally effective. Radical pairs generated by the photolysis of diacylperoxide also exhibited substantial surface mobility.<sup>29</sup>

Anpo et al have studied the photolysis of several alkylketones adsorbed on the porous Vycor glass.<sup>30</sup> The

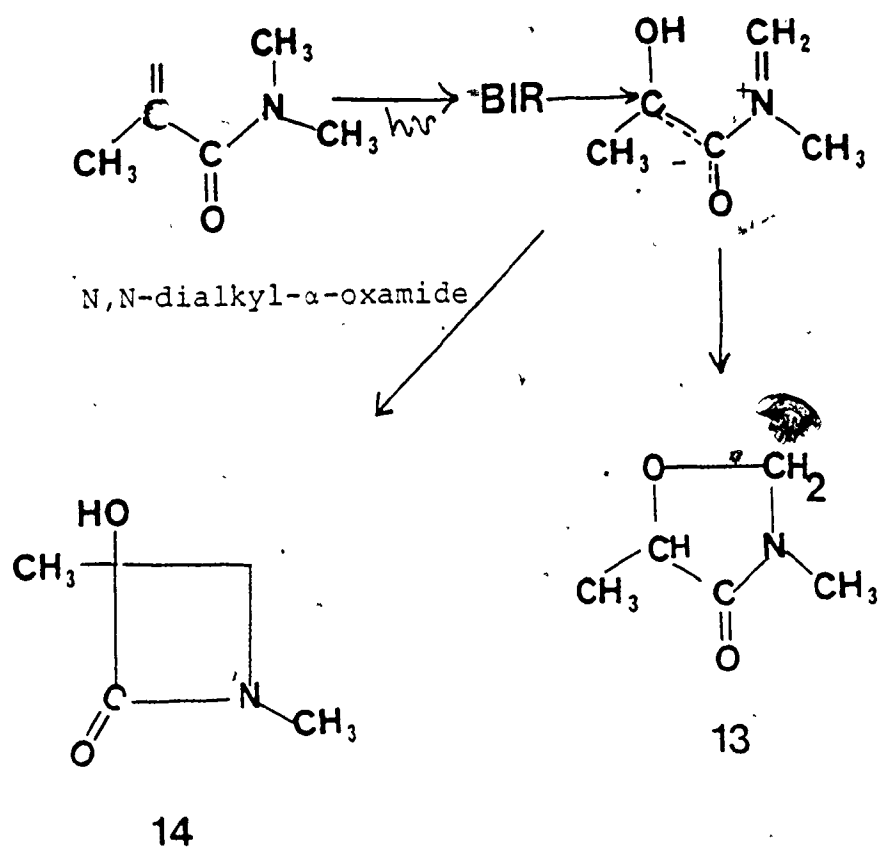
ratio of type I/type II decreased with increasing degassing temperature i.e. with decreasing surface polarity owing to the decrease in the concentration of surface hydroxyls.

#### 1.6 UNIMOLECULAR REACTIONS OF ADSORBED MOLECULES

Leermakers observed that the photostationary state (PSS) of E/Z isomerization of stilbene was affected by adsorption on a silica gel slurry.<sup>31</sup> The (PSS) of photochromic spiropyrans was claimed to be strongly affected by adsorption.<sup>32</sup> These effects were attributed to the specific bonding interaction with the silica gel surface.<sup>13</sup>

Photoisomerization of thioindigo adsorbed on alumina was examined.<sup>16</sup> While trans-cis isomerization was readily induced by irradiation, cis-thioindigo was stable at the alumina surface and could not be back converted to the trans isomer. The irradiation of trans-stilbene on neutral alumina produced a photochromic change that was largely reversible on standing.<sup>33,34</sup> The photocyclization of phenylethylenes to dihydrophenanthrenes adsorbed on alumina was attributed to the surface assisted orientation of two aromatic rings to planar configuration from which the photocyclization proceeded.<sup>35</sup> Isomerization of cis-2 butene, caused by electronically excited SO<sub>2</sub> adsorbed on porous Vycor glass have been also reported.<sup>36</sup>

Recently, Ellis has reported the silica gel slurry mediated photoisomerization of all-trans retinal



Scheme V

isomers.<sup>37</sup> The 11-cis retinal isomer was not found when all-trans retinal was photolysed in non-polar solvents. Prolonged irradiation on silica gel gave a mixture of four isomers i.e. (pss) and was richest in 11-cis retinal, which constituted -35% of this mixture. The difference in reactivity was attributed to state switching, analogous to the behaviour in polar solvents. The quantum yield ( $\phi_a$  11-cis  $\rightarrow$  all-trans) was 7 times larger on silica than in alcoholic solvents. It was attributed to the inhomogeneity of the silica gel surface, e.g., local variation in silanol density which influenced the excited state reactivity or pereturbed the efficiency of an excited-state process.

The photolysis of N,N-dialkyl- $\alpha$ -oxamide<sup>38</sup> in acidic methanol and on silica gel resulted in the exclusive formation of oxazolidinone 13. Irradiation of N,N-dialkyl- $\alpha$ -oxamide, when included in the crystals of desoxycholic acid gave  $\beta$ -lactam 14, as the only product (Scheme V). The author has proposed the intermediacy of a zwitterion in the reaction mechanism. In the solid state, the molecular motion of the amide was restricted and gave only the  $\beta$ -lactam 14. The absence of  $\beta$ -lactam on silica gel clearly indicated that molecular motion in the intermediate zwitterion was not restricted.

The photochlorination of stearic acid in solution showed a preferential attack at  $\beta$  position. On the other hand, stearic acid adsorbed on alumina photochlorinated at the terminal methyl group.<sup>39</sup> The greater susceptibility to

photochlorination for terminal methyl was attributed to the alignment of the densely packed carboxylic acid in such a way, as to have the acid group attached to the alumina surface with the aliphatic chain perpendicular to it.

### 1.7 BIMOLECULAR REACTIONS OF ADSORBED MOLECULES

There are very few examples of bimolecular reactions of adsorbed molecules. The irradiation of 2-methyl-1,4-napthoquinone in a silica-chloroform slurry resulted in the formation of four different cyclobutane-dimers. In contrast, its irradiation in the solid state gave only the syn head-head and head-tail dimers.<sup>40</sup>

The photodimerization of 3-methyl-4-nitro-5-styrylisoxazole on dry silica or silica gel-cyclohexane slurry led to the formation of four cyclobutane-dimers, as obtained from solution irradiation but in different ratios.<sup>41</sup> On the other hand, in the solid state it gave only one dimer. These results clearly indicated that silica gel allowed greater freedom to an intermediate 1,4-biradical than in the solid state.

In order to demonstrate that translational movement (inter- and intragranular) in the life time of the excited state occurs in medium sized closed shell organic molecules on the silica gel surface de Mayo has provided photochemical and photophysical evidence in his recent studies concerning translational movement of adsorbed

acenaphthylene and 9-cyanophenanthrene on dry silica gel.<sup>42,43</sup> The irradiation of acenaphthylene in solution and on dry silica gel gave cis and trans cyclobutane dimers. The cis:trans ratio varied with surface coverage. Triplet quenching and coadsorption of structurally similar acenaphthene studies indicated that the singlet (life time  $\sim 1$  ns) reacted only with its nearest immediate neighbours. The long lived triplet had time for migration before reaction. The dimerization was sensitized with Rose Bengal ( $\sim 0.1\%$  coverage). At 10% conversion, 1 molecule sensitized  $> 57$  molecules of acenaphthylene, which would require translational motion of both monomer and cyclobutane dimer to occur. It was claimed from quenching studies that acenaphthylene moved  $\sim 2\text{\AA}$  during the singlet life time and  $300\text{\AA}$  during its triplet life time. Dimerization of 9-cyanophenanthrene has been also carried out by de Mayo and coworkers. The longer singlet life time of 9-cyanophenanthrene as compared to acenaphthylene allowed movement to occur in the bimolecular reaction of the former in its singlet excited state. In summary, these results clearly indicated that bimolecular reactions of adsorbed molecules do occur.

#### 1.8 SCOPE OF THE PRESENT INVESTIGATION

This section of the thesis is an account of the results derived from the investigation into the feasibility of using a dry surface (silica gel or alumina) to bring

about a change in the stereochemistry of photocycloaddition of enones to alkenes and allene. A brief review of the mechanism and the stereochemistry of enone photocycloaddition as well as reasons for the choice of substrates has been presented in Chapter 2.

## CHAPTER 2

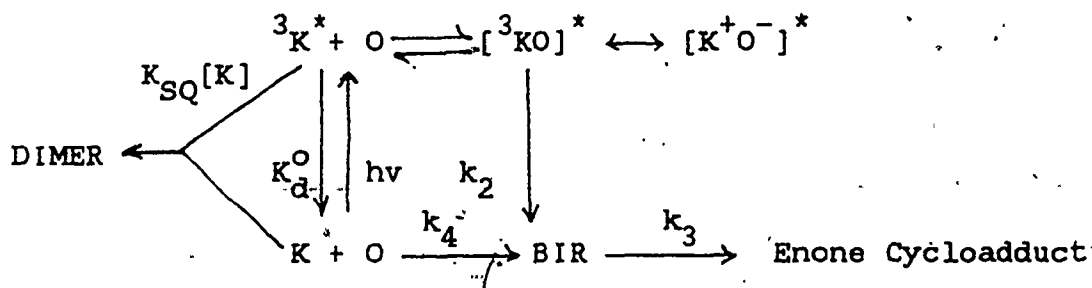
### ENONE PHOTOCYCLOADDITION BY ADSORBED MOLECULES ON SILICA GEL AND ALUMINA

#### ENONE PHOTOCYCLOADDITION

The light induced addition of a double bond to an  $\alpha,\beta$ -unsaturated ketone to give a cyclobutane is referred to as an enone photocycloaddition. The general reaction has received considerable attention and various informative reviews have appeared.<sup>44-48</sup> The synthetic aspects of this useful reaction will be discussed in chapter 5.

#### 2.1 THE REACTION MECHANISM

Several detailed reviews regarding the reaction mechanism of enone photocycloaddition have appeared<sup>44-48</sup> and will be briefly summarized here. The generally accepted model for this reaction is shown in Scheme VI.



K = enone, O = olefin,  $3K^*$  = triplet excited state of enone,  $^3[KO]^*$  = triplet exciplex intermediate, BIR = Biradical intermediate

SCHEME VI



The absorption of light by the enone results in formation of the singlet excited state,  $^1K^*$ . In flexible systems (i.e., acyclic enones), this can apparently decay rapidly to the ground state by cis-trans isomerization of the double bond and no other reaction is observed. In less flexible enones (e.g., cyclic enones), intersystem crossing competes to give the triplet excited state,  $^3K^*$ , with a quantum yield approaching unity in the case of cyclohexenone and cyclopentenone.<sup>50</sup> The triplet excited state is sufficiently long lived in the cyclic enones that bimolecular processes such as enone photocycloaddition can compete with non-diffusional processes ( $K_d^0$ ) leading to deactivation of the excited state. This enone triplet excited state can undergo quenching by ground state enone molecules to give dimer<sup>51</sup> or by any other quencher in the system, provided it has a lower triplet energy, or form an excited complex (exciplex) with alkenes. The idea of the participation of an exciplex ( $\pi$  complex) was originally proposed by Corey.<sup>52</sup> The evidence for its formation is indirect, and it was originally proposed as an intermediate to rationalize the regiochemical outcome of enone photocycloaddition.<sup>52</sup> The orientation of this  $\pi$  complex is reflected in the regiochemistry of the cycloadduct. Corey proposed that the more favourable orientation of the  $\pi$  complex is that in which the dipole of the alkene is opposed to that of the excited ketone. The cases in which this rule breaks down can usually be accounted for by

unfavourable steric interactions between enone and alkene in the more stable  $\pi$  complex orientation.

Loutfy and de Mayo<sup>49</sup> showed that the exciplex was formed irreversibly with a rate constant of  $8.24 \times 10^8 \text{ L mol}^{-1} \text{ sec}^{-1}$  for the cyclopentenone-cyclohexene reaction and  $3.3 \times 10^8 \text{ L mol}^{-1} \text{ sec}^{-1}$  for the cyclohexenone-cyclohexene reaction at 293K. The activation energies for these processes were 1.3 and 0.9 kcal/mol, respectively. The difference in reaction rates between these two systems was explained in terms of the changes in the preexponential factors in the Arrhenius equation. This has been explained in terms of the flexible nature of the triplet excited state of the cyclohexenone,<sup>53</sup> and hence its inability to attain the appropriate orientation for formation of the exciplex.

The resulting exciplex can collapse to the biradical intermediate (BIR); which can undergo fission to give back the starting materials or cyclize to give the cyclobutane products. The reversion of the biradical intermediate to starting material is the main source of inefficiency in the photocycloaddition. The evidence for the intermediacy of the 1,4 biradical comes from studies of the products of enone photocycloaddition. The by-products frequently observed are the "ene" products, which arise from intramolecular hydrogen abstraction through a six-centered transition state in the intermediate 1,4 biradical.

The other evidence for the intermediacy of the 1,4

biradical comes from the observation of isomerization of unreacted olefin and the formation of a similar mixture of cyclobutane products either starting from pure cis or pure trans olefin.<sup>55</sup> It is believed that the stereochemistry of the olefin is lost in the cyclobutane products because of rotational equilibration in the intermediate 1,4 biradical.

## 2.2 ELECTRONIC NATURE OF ENONE TRIPLET

The two lowest spectroscopic states in the enone manifold are  $n\pi^*$  and  $\pi\pi^*$ . Theoretical studies have clearly indicated that the  $n\pi^*$  state relaxes by bond stretching while remaining planar, whereas the  $\pi\pi^*$  state relaxes largely by rotation around the C<sub>2</sub>-C<sub>3</sub> bond and by out of plane deformation of the H-C<sub>2</sub> bond in addition to bond stretching.<sup>53,56a</sup> Recently, Schuster has also shown that the twisted  $^3\pi\pi^*$  excited state is responsible for photocycloaddition.<sup>56b</sup> Calculation suggests that the triplet  $n\pi^*$  and  $\pi\pi^*$  states are much closer in energy and that a state inversion may occur resulting in the  $\pi\pi^*$  state having lower energy.<sup>57a</sup> Schaffner showed that the low lying emitting state of testosterone was  $^3\pi\pi^*$  with a quantum yield of phosphorescence  $\phi_p = 0.21$  and life time of 58 ns.<sup>57b</sup> The observed life time was short for the  $^3\pi\pi^*$  state and long for the  $^3n\pi^*$ . This result was attributed to the vibronic coupling between these two states which have very similar triplet energy.

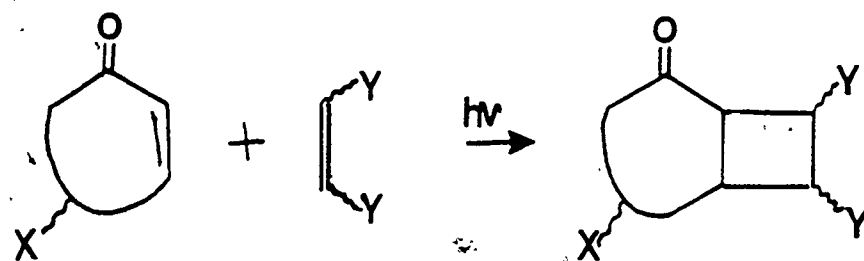
2

### 2.3 STEREOCHEMICAL CONSIDERATIONS

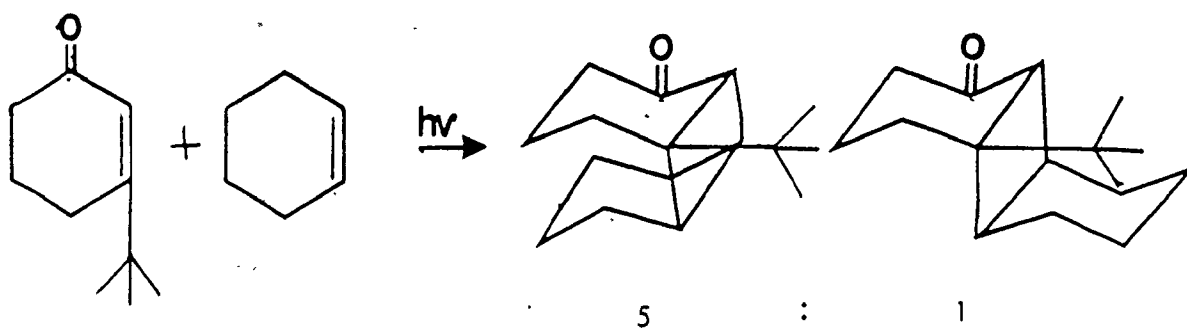
In designing a synthetic route incorporating enone photocycloaddition as a synthetic step the knowledge of factors which govern the regiochemistry and stereochemistry of cyclobutane formation are of prime importance.

The regiochemistry has been altered or enhanced in some cases by placing directing groups on the enone or alkene which were later removed.<sup>58a</sup> de Mayo and coworkers have altered or reversed the regiochemical outcome of enone photocycloaddition in a number of cycloadducts by performing the reaction in micellar media.<sup>58b</sup> The lack of control of regioselectivity in enone photocycloaddition has been a limiting factor in its application in synthesis. To some extent solvents can be used to alter the product ratio; however, this is usually only capable of enhancing the observed regioselectivity rather than reversing it.<sup>58c</sup>

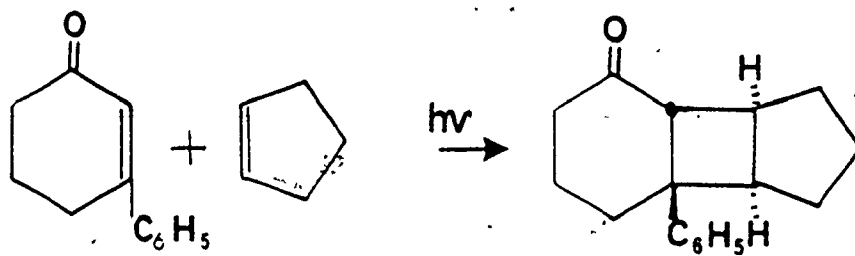
The situation regarding stereochemistry is potentially more complicated than with regiochemistry. Intermediacy of a 1,4 biradical has rendered the control of stereochemistry in this useful reaction difficult. Various stereochemical possibilities exist in the photocycloaddition of cyclic enones with acyclic olefins (e.g., Scheme VII). The cyclic enone-cyclobutane ring junction can be cis or trans. The substituents on the alkene can be endo or exo oriented, cis or trans with respect to each other. In the case of enone photocycloaddition with cyclic olefins the two rings can be syn or anti with respect to each other (e.g., Scheme VIII).



Scheme VII



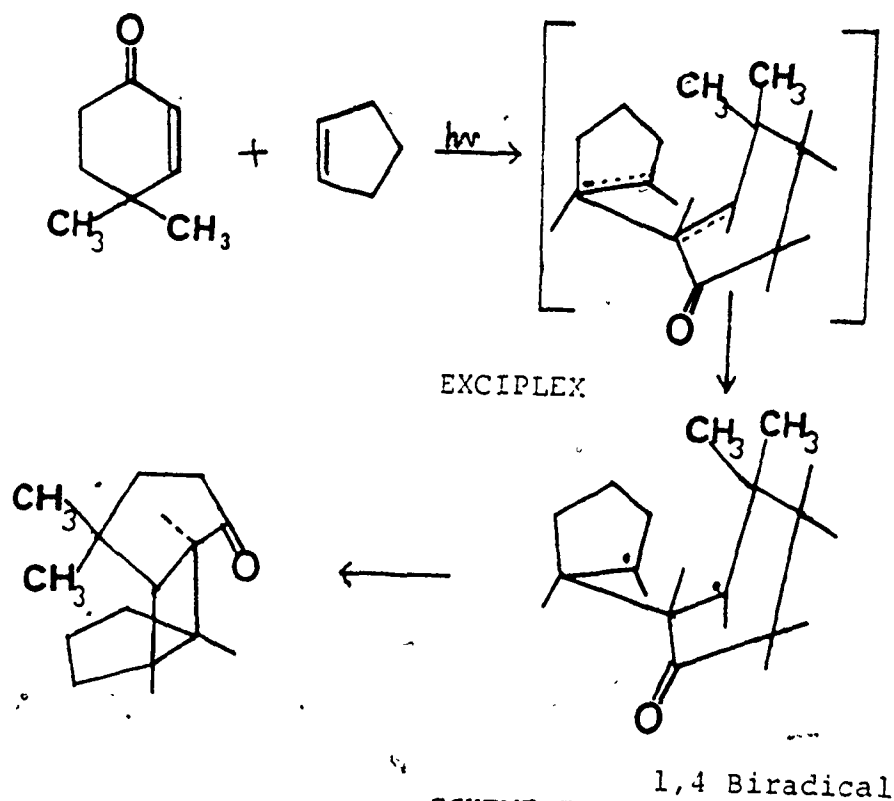
ref. 60



ref. 61

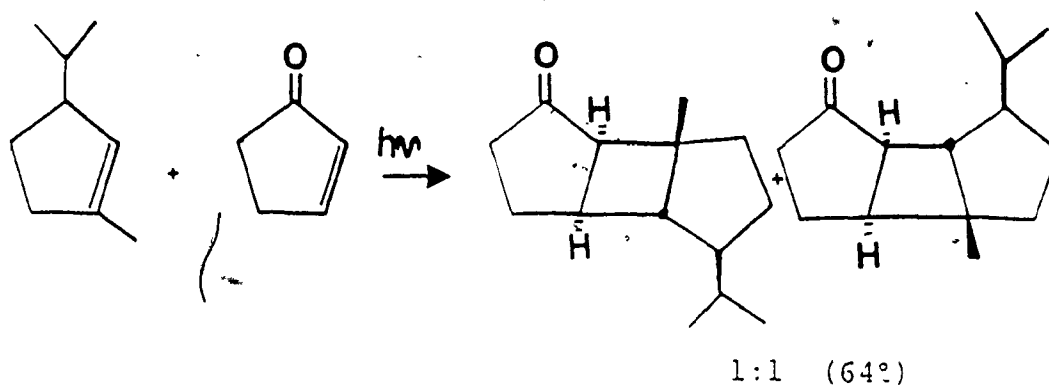
Scheme VIII

The formation of higher energy trans products from cyclohexenone and simple alkenes has been generally rationalized by assuming that the enone in its excited state is twisted about the carbon-carbon double bond and this twisting is conserved for a short period as 1,4 biradical giving trans product by rapid closure of the biradical.<sup>44,59</sup> On the other hand, conformational relaxation preceding the closure of the biradical would give the cis product. Based on de Mayo's arguments<sup>44</sup> McCullough explained the formation of the trans product and also suggested on steric grounds that the initial bond formation was near the carbonyl group as shown in Scheme IX.<sup>59</sup>



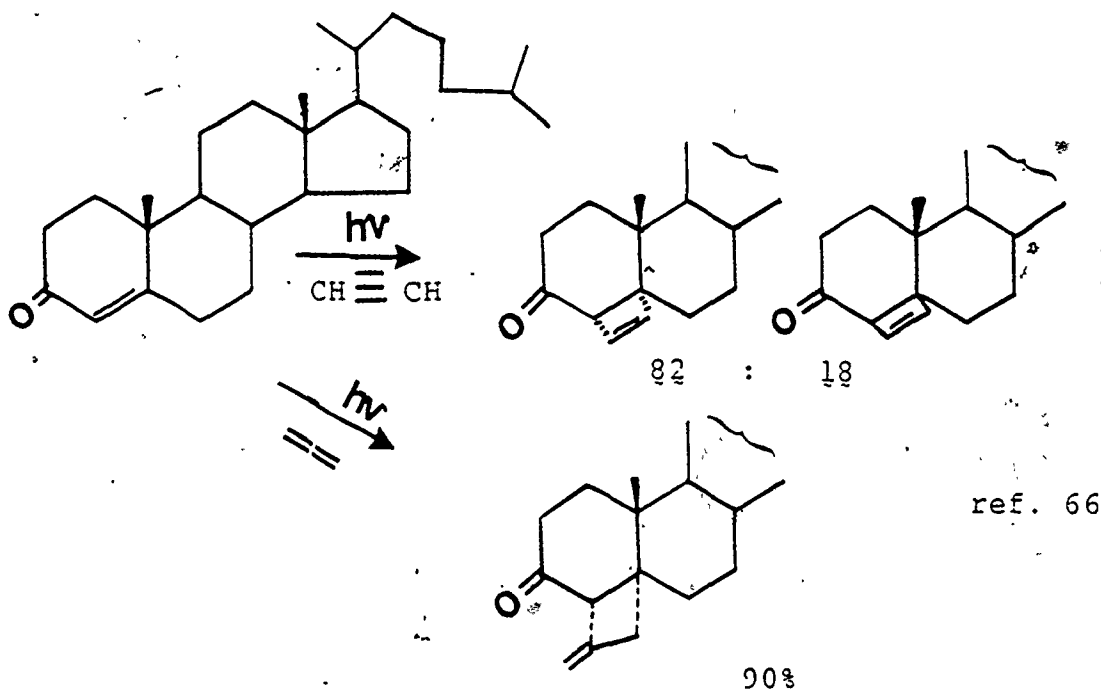
Generally, by carefully choosing the substrates (enone and alkene) the stereochemical outcome of the photocycloadduct can be predicted. The following general statements concerning stereochemistry can be made: In the photocycloaddition of cyclopentenone to alkenes the ring junction is always cis. Similarly, in the photo-cycloaddition of cyclohexenone to alkyne, cyclobutene ring fusion is also cis. In the products from addition of cyclohexenone with alkenes (except allene, alkynes and cyclobutene) the ring junction can be cis or trans. In cycloadducts where enone and olefin are fused cis, the two rings are generally anti to each other. In general, the 1,4 biradical, owing to strain, can only close to give cis fused products in the case of rigid enones (cyclopentenone) and rigid alkenes (allene and cyclobutene).

When the two face of the double bond in the alkene are nonequivalent the major product generally arises from the attack of enone on the less hindered side of the alkene (Scheme X).<sup>62</sup>



Scheme X

Similarly, with enones when the two faces are nonequivalent the attack by olefin is largely from the less hindered side of the enone. (Scheme XI).<sup>63-69</sup>



Scheme XI.

Some years ago, Wiesner proposed<sup>70</sup> that the stereochemistry of the enone cycloaddition to alkenes or allene could be predicted from a presumed conformational posture of the enone excited state, and an initial, assumed bond formation at the  $\beta$  carbon: this resultant stereochemistry might or might not derive from the steric ease of approach of the olefin. A detailed discussion will be presented in Chapter 3.

#### 2.4 CHOICE OF SUBSTRATE

A steroidal enone has a nearly flat overall structure, but has different steric features on its two faces, thus



rendering approach to the double bond in photocycloaddition susceptible, in principle to steric control. An example involving a steroidal enone is illustrated in Scheme XI. These steroidal enones seemed suitable for the study of specific steric effects on the process of photocycloaddition, particularly if the ease of approach was capable of modification. One technique that seemed suitable to achieve this modification was that of prior adsorption of the reactants on a surface (silica gel or alumina).

The substrates used were steroidal enones (15a-15c, 24, 26, 30b and 31), chosen because it was hoped that these large flat molecules with two polar functional groups would assume a position with its less hindered  $\alpha$  face towards the bulk of the gel (silica or alumina) leaving the normally more hindered  $\beta$  side open to attack. The principal binding was presumed to be hydrogen bonding to the ketone lone pair, the main bulk of the molecule being held down by  $\pi$  bonding to the double bond, with contributions from other polar functions that might be also present elsewhere in the molecule since, for effective hindrance, 'single point' bonding must surely be inadequate.

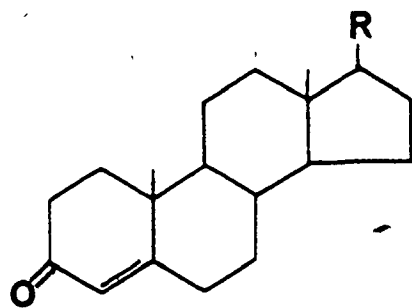
For comparison, the photocycloaddition was carried out in methanolic solution. Methanol was chosen as the polar solvent to minimize or reduce the effect of the local polarity of silica gel, since it has been shown by Leermaker that silica gel approximates methanol on the

Kosower Z scale.<sup>13,21</sup>

## RESULTS AND DISCUSSION

### 2.5 Photocycloaddition of testosterone propionate (15a) to ethylene

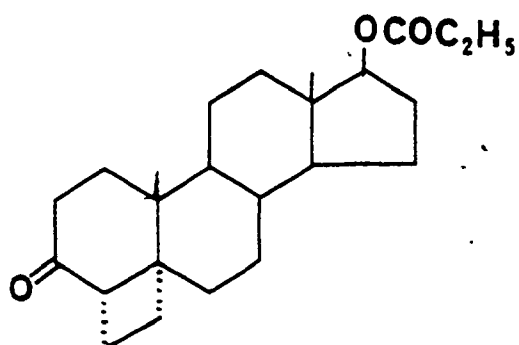
The photocycloaddition of testosterone propionate 15a to ethylene in methanol was carried out by the procedure of Rubin<sup>63</sup> to give the 4 $\alpha$ ,5 $\alpha$  (16a) and 4 $\alpha$ ,5 $\beta$  (16c) isomers as major photocycloadducts: in addition the 4 $\beta$ ,5 $\beta$  isomer, 16b, was detected as a minor adduct by HPLC analysis. Analysis by G.C. of the irradiation mixture was complicated by the fact that the 4 $\alpha$ ,5 $\beta$  isomer, 16c, isomerised to 4 $\beta$ ,5 $\beta$  isomer, 16b, at the required column temperature of 230°C. The photocycloaddition of 15a to ethylene in ethyl acetate again gave 16a and 16c as major cycloadducts, together with 16b (4 $\beta$ ,5 $\beta$ ), previously unreported,<sup>63</sup> in minor amount. The irradiation products were separated by flash chromatography to give 4 $\alpha$ ,5 $\alpha$  isomer (16a) in -24% yield. The <sup>1</sup>Hmr spectrum of this compound exhibited a singlet due to the C-19 angular methyl at 0.83 ppm. The calculated chemical shift of the C-19 methyl resonance using additive rules is 0.96 ppm.<sup>63</sup> The substantial shift observed was attributed to the C-19 methyl group experiencing the shielding effects of the 3-carbonyl in the distorted A ring (boat or twist form).<sup>63</sup> The mass spectrum possessed the correct molecular ion at 372 mass units. It had a m.p. identical with that reported in the literature.



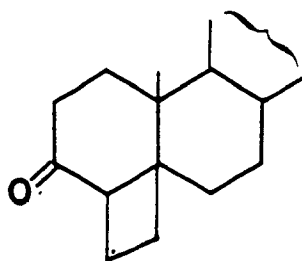
15a  $R = -OCOC_2H_5$

15b  $= \beta \text{ OH}$

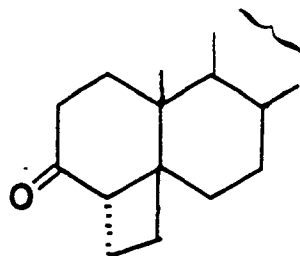
15c  $= \alpha \text{ OH}$



16a



16b



16c

The second isomer (16c) off the column possessed a trans 6/4 ring junction. It also had a m.p. identical with that reported in literature. The mass spectrum contained an expected molecular ion at 372 mass units. Confirmatory evidence for the trans-stereochemical assignment was obtained by the reported thermal isomerization to the cis 4 $\beta$ ,5 $\beta$  adduct (16b).<sup>63</sup>

The third isomer 4 $\beta$ ,5 $\beta$  (16b) possessed an identical R<sub>f</sub> with 4 $\alpha$ ,5 $\alpha$  (16a) on t.l.c. This previously unreported isomer<sup>63</sup> was isolated in minor amount by flash chromatography. HPLC analysis of 16b on  $\mu$  Porasil silica column showed it to be containing 10% of 16a as an impurity. The stereochemistry at the ring junction was assigned as 4 $\beta$ ,5 $\beta$ , on the basis of a (-Ve) Cotton effect in the circular dichroism (CD) spectrum. The mass spectrum (M<sup>+</sup>372) indicated the addition of ethylene molecule to 15a.

In contrast, irradiation of 15a and ethylene on silica gel resulted in preferential attack on the  $\beta$  face. In addition, the yield of 16c (trans-isomer) was reduced to trace amounts. Since the formation of trans fused systems require conformational inversion in the intermediate 1,4 biradical,<sup>44,47</sup> the effect of lowering the temperature was investigated. At low temperature in methanol  $\alpha$  addition was favoured by -7:1, whereas on silica gel at the same temperature  $\beta$  addition was favoured (Table 2.1). Both low temperature and adsorption on silica gel apparently disfavour the inversion required for the formation of

TABLE 2.1. CONDITIONS<sup>a,b</sup> AND THE RESULTS OF THE CYCLOADDITION OF ENONES TO ALKENES OR ALLENE.

Enone	alkenes	temp(°C)	Time	System	Conversion(%)	Yield(%)	product <sup>d</sup>	isomer(%)		
								4a5a	4p5p	4a5p
15a	ethylene	11	1 hr	CH <sub>3</sub> OH	57		16a, 16b, 16c <sup>e</sup>	57	10	32
		11	4 hr	EtOAc	90		16a, 16b, 16c	67	33	f
		-70	1 hr 10 min	CH <sub>3</sub> OH	24		16a, 16b, 16c <sup>e</sup>	82	12	6
		-70	4 hr	EtOAc	100		16a, 16b, 16c	87	13	f
		11	4 hr	SiO <sub>2</sub>	100		16a, 16b, 16c <sup>e</sup>	49	51	trace
		-70	6 hr	SiO <sub>2</sub>	96		16a, 16b, 16c <sup>e</sup>	42	58	trace
		8	1 hr 40 min	CH <sub>3</sub> OH	61		17a, 17b, 17c	46	22	31 <sup>f</sup>
		8	3 hr	Cyclopentene	100	53.6 (32.6)	17a, 17b, 17c	35.5 (28) <sup>g</sup>	15.5 (0) <sup>g</sup>	48.8 <sup>f</sup> (72) <sup>g</sup>
		-70	1 hr 50 min	CH <sub>3</sub> OH	67		17a, 17b, 17c	53	41	6 <sup>f</sup>
		11	3 hr 11 min	SiO <sub>2</sub>	46	52	17a, 17b, 17c	33	56	10 <sup>f</sup>
allene	allene	-70	7 hr 30 min	SiO <sub>2</sub>	66		17a, 17b, 17c	32	57	10 <sup>f</sup>
		11	30 min	CH <sub>3</sub> OH	58		18a, 18b	83	17	
		11	4 hr 15 min	EtOAc	100		18a, 18b	84.4	15.6	
		-78	1 hr	CH <sub>3</sub> OH	75		18a, 18b	90	10	
		-78	1 hr	EtOAc	100		18a, 18b	89	11	
		11	2 hr, 4 hr 15 min	SiO <sub>2</sub>	80, 100	85	18a, 18b, 18c	46, 47 <sup>g</sup>	54, 53 <sup>g,h</sup>	
		-78	3 hr	SiO <sub>2</sub>	97		18a, 18b, 18c	47	53	
		11	3 hr	Al <sub>2</sub> O <sub>3</sub>	80		18a, 18b, 18c	20	80	
		20	1 hr 30 min	CH <sub>3</sub> OH	73		19a, 19b <sup>i</sup>	82	18	
		20	6 hr	SiO <sub>2</sub>	85		19a, 19b, 19c <sup>i</sup>	59	41	
15b	allene	20	6 hr	Al <sub>2</sub> O <sub>3</sub>	80		19a, 19b, 19c <sup>i</sup>	61	39	
15c	allene	-70	45 min	CH <sub>3</sub> OH	100		19a, 19b <sup>j</sup>	91.5	8.5	
		20	1 hr 30 min	SiO <sub>2</sub>	100		19a, 19b, 19c <sup>j</sup>	34	66	
		20	45 min	Al <sub>2</sub> O <sub>3</sub>	100		19a, 19b, 19c <sup>j</sup>	6	94	

24	allene	-70	1 hr 15 min	CH <sub>3</sub> OH	95	52.6	25a, 25b	78, 86	22, 148	
		20	5 hr	SiO <sub>2</sub>	100		25a, 25b	58.5	41.5	
26	cyclopentene	20		C <sub>6</sub> H <sub>6</sub>	90	(82.2) <sup>k</sup>	27a			(100) <sup>k</sup>
		20	18 hr	SiO <sub>2</sub>	55	57	27a, 27b			66.5 <sup>l</sup> 28 <sup>m</sup>

isomer(%)

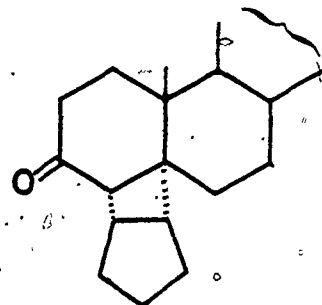
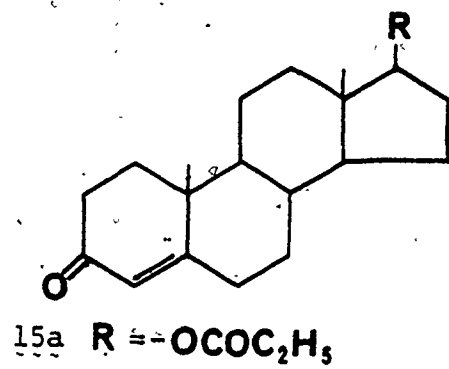
Enone	alkenes	temp(°C)	Time	System	Conversion(%)	Yield(%)	product	16a/17a	16a/17b
31a	ethylene	11	2 hr	CH <sub>3</sub> OH	55		32a, 32b	95	5
		-70	2 hr	CH <sub>3</sub> OH	20		32a, 32b	94.5	3.5
		11	4 hr, 18 hr	SiO <sub>2</sub>	70	50	32a, 32b	56, 60	44, 40
		-70	3 hr 30 min	SiO <sub>2</sub>	86		32a, 32b	54.5	44.5
31b	ethylene	20	3 hr	CH <sub>3</sub> OH	60		32a, 32b, <sup>n</sup>	96	4
		20	4 hr, 10 min	SiO <sub>2</sub>	66.5		32a, 32b, <sup>n</sup>	5	45

2450 W medium pressure Hg lamp; 0.1 mmol of enone and 1 mmol of alkene or allene on 3 g of silica gel or alumina; isolated yield (based on the recovered starting material) of cycloadducts after chromatography, literature values in parentheses; the cycloadducts from the irradiation of 15c and 31b with allene were not isolated due to limited availability of the expensive steroid; the quantitative separation of 16b and 16c from the irradiation mixture of 15a and ethylene was rendered difficult due to their identical R<sub>f</sub> values on tlc; analyses of 31c, 31d, 31e, 31f, 31g, 31h, 31i, 31j, 31k, 31l, 31m, 31n, 31o, 31p, 31q, 31r, 31s, 31t, 31u, 31v, 31w, 31x, 31y, 31z, 32a, 32b, 32c, 32d, 32e, 32f, 32g, 32h, 32i, 32j, 32k, 32l, 32m, 32n, 32o, 32p, 32q, 32r, 32s, 32t, 32u, 32v, 32w, 32x, 32y, 32z, 33a, 33b, 33c, 33d, 33e, 33f, 33g, 33h, 33i, 33j, 33k, 33l, 33m, 33n, 33o, 33p, 33q, 33r, 33s, 33t, 33u, 33v, 33w, 33x, 33y, 33z, 34a, 34b, 34c, 34d, 34e, 34f, 34g, 34h, 34i, 34j, 34k, 34l, 34m, 34n, 34o, 34p, 34q, 34r, 34s, 34t, 34u, 34v, 34w, 34x, 34y, 34z, 35a, 35b, 35c, 35d, 35e, 35f, 35g, 35h, 35i, 35j, 35k, 35l, 35m, 35n, 35o, 35p, 35q, 35r, 35s, 35t, 35u, 35v, 35w, 35x, 35y, 35z, 36a, 36b, 36c, 36d, 36e, 36f, 36g, 36h, 36i, 36j, 36k, 36l, 36m, 36n, 36o, 36p, 36q, 36r, 36s, 36t, 36u, 36v, 36w, 36x, 36y, 36z, 37a, 37b, 37c, 37d, 37e, 37f, 37g, 37h, 37i, 37j, 37k, 37l, 37m, 37n, 37o, 37p, 37q, 37r, 37s, 37t, 37u, 37v, 37w, 37x, 37y, 37z, 38a, 38b, 38c, 38d, 38e, 38f, 38g, 38h, 38i, 38j, 38k, 38l, 38m, 38n, 38o, 38p, 38q, 38r, 38s, 38t, 38u, 38v, 38w, 38x, 38y, 38z, 39a, 39b, 39c, 39d, 39e, 39f, 39g, 39h, 39i, 39j, 39k, 39l, 39m, 39n, 39o, 39p, 39q, 39r, 39s, 39t, 39u, 39v, 39w, 39x, 39y, 39z, 40a, 40b, 40c, 40d, 40e, 40f, 40g, 40h, 40i, 40j, 40k, 40l, 40m, 40n, 40o, 40p, 40q, 40r, 40s, 40t, 40u, 40v, 40w, 40x, 40y, 40z, 41a, 41b, 41c, 41d, 41e, 41f, 41g, 41h, 41i, 41j, 41k, 41l, 41m, 41n, 41o, 41p, 41q, 41r, 41s, 41t, 41u, 41v, 41w, 41x, 41y, 41z, 42a, 42b, 42c, 42d, 42e, 42f, 42g, 42h, 42i, 42j, 42k, 42l, 42m, 42n, 42o, 42p, 42q, 42r, 42s, 42t, 42u, 42v, 42w, 42x, 42y, 42z, 43a, 43b, 43c, 43d, 43e, 43f, 43g, 43h, 43i, 43j, 43k, 43l, 43m, 43n, 43o, 43p, 43q, 43r, 43s, 43t, 43u, 43v, 43w, 43x, 43y, 43z, 44a, 44b, 44c, 44d, 44e, 44f, 44g, 44h, 44i, 44j, 44k, 44l, 44m, 44n, 44o, 44p, 44q, 44r, 44s, 44t, 44u, 44v, 44w, 44x, 44y, 44z, 45a, 45b, 45c, 45d, 45e, 45f, 45g, 45h, 45i, 45j, 45k, 45l, 45m, 45n, 45o, 45p, 45q, 45r, 45s, 45t, 45u, 45v, 45w, 45x, 45y, 45z, 46a, 46b, 46c, 46d, 46e, 46f, 46g, 46h, 46i, 46j, 46k, 46l, 46m, 46n, 46o, 46p, 46q, 46r, 46s, 46t, 46u, 46v, 46w, 46x, 46y, 46z, 47a, 47b, 47c, 47d, 47e, 47f, 47g, 47h, 47i, 47j, 47k, 47l, 47m, 47n, 47o, 47p, 47q, 47r, 47s, 47t, 47u, 47v, 47w, 47x, 47y, 47z, 48a, 48b, 48c, 48d, 48e, 48f, 48g, 48h, 48i, 48j, 48k, 48l, 48m, 48n, 48o, 48p, 48q, 48r, 48s, 48t, 48u, 48v, 48w, 48x, 48y, 48z, 49a, 49b, 49c, 49d, 49e, 49f, 49g, 49h, 49i, 49j, 49k, 49l, 49m, 49n, 49o, 49p, 49q, 49r, 49s, 49t, 49u, 49v, 49w, 49x, 49y, 49z, 50a, 50b, 50c, 50d, 50e, 50f, 50g, 50h, 50i, 50j, 50k, 50l, 50m, 50n, 50o, 50p, 50q, 50r, 50s, 50t, 50u, 50v, 50w, 50x, 50y, 50z, 51a, 51b, 51c, 51d, 51e, 51f, 51g, 51h, 51i, 51j, 51k, 51l, 51m, 51n, 51o, 51p, 51q, 51r, 51s, 51t, 51u, 51v, 51w, 51x, 51y, 51z, 52a, 52b, 52c, 52d, 52e, 52f, 52g, 52h, 52i, 52j, 52k, 52l, 52m, 52n, 52o, 52p, 52q, 52r, 52s, 52t, 52u, 52v, 52w, 52x, 52y, 52z, 53a, 53b, 53c, 53d, 53e, 53f, 53g, 53h, 53i, 53j, 53k, 53l, 53m, 53n, 53o, 53p, 53q, 53r, 53s, 53t, 53u, 53v, 53w, 53x, 53y, 53z, 54a, 54b, 54c, 54d, 54e, 54f, 54g, 54h, 54i, 54j, 54k, 54l, 54m, 54n, 54o, 54p, 54q, 54r, 54s, 54t, 54u, 54v, 54w, 54x, 54y, 54z, 55a, 55b, 55c, 55d, 55e, 55f, 55g, 55h, 55i, 55j, 55k, 55l, 55m, 55n, 55o, 55p, 55q, 55r, 55s, 55t, 55u, 55v, 55w, 55x, 55y, 55z, 56a, 56b, 56c, 56d, 56e, 56f, 56g, 56h, 56i, 56j, 56k, 56l, 56m, 56n, 56o, 56p, 56q, 56r, 56s, 56t, 56u, 56v, 56w, 56x, 56y, 56z, 57a, 57b, 57c, 57d, 57e, 57f, 57g, 57h, 57i, 57j, 57k, 57l, 57m, 57n, 57o, 57p, 57q, 57r, 57s, 57t, 57u, 57v, 57w, 57x, 57y, 57z, 58a, 58b, 58c, 58d, 58e, 58f, 58g, 58h, 58i, 58j, 58k, 58l, 58m, 58n, 58o, 58p, 58q, 58r, 58s, 58t, 58u, 58v, 58w, 58x, 58y, 58z, 59a, 59b, 59c, 59d, 59e, 59f, 59g, 59h, 59i, 59j, 59k, 59l, 59m, 59n, 59o, 59p, 59q, 59r, 59s, 59t, 59u, 59v, 59w, 59x, 59y, 59z, 60a, 60b, 60c, 60d, 60e, 60f, 60g, 60h, 60i, 60j, 60k, 60l, 60m, 60n, 60o, 60p, 60q, 60r, 60s, 60t, 60u, 60v, 60w, 60x, 60y, 60z, 61a, 61b, 61c, 61d, 61e, 61f, 61g, 61h, 61i, 61j, 61k, 61l, 61m, 61n, 61o, 61p, 61q, 61r, 61s, 61t, 61u, 61v, 61w, 61x, 61y, 61z, 62a, 62b, 62c, 62d, 62e, 62f, 62g, 62h, 62i, 62j, 62k, 62l, 62m, 62n, 62o, 62p, 62q, 62r, 62s, 62t, 62u, 62v, 62w, 62x, 62y, 62z, 63a, 63b, 63c, 63d, 63e, 63f, 63g, 63h, 63i, 63j, 63k, 63l, 63m, 63n, 63o, 63p, 63q, 63r, 63s, 63t, 63u, 63v, 63w, 63x, 63y, 63z, 64a, 64b, 64c, 64d, 64e, 64f, 64g, 64h, 64i, 64j, 64k, 64l, 64m, 64n, 64o, 64p, 64q, 64r, 64s, 64t, 64u, 64v, 64w, 64x, 64y, 64z, 65a, 65b, 65c, 65d, 65e, 65f, 65g, 65h, 65i, 65j, 65k, 65l, 65m, 65n, 65o, 65p, 65q, 65r, 65s, 65t, 65u, 65v, 65w, 65x, 65y, 65z, 66a, 66b, 66c, 66d, 66e, 66f, 66g, 66h, 66i, 66j, 66k, 66l, 66m, 66n, 66o, 66p, 66q, 66r, 66s, 66t, 66u, 66v, 66w, 66x, 66y, 66z, 67a, 67b, 67c, 67d, 67e, 67f, 67g, 67h, 67i, 67j, 67k, 67l, 67m, 67n, 67o, 67p, 67q, 67r, 67s, 67t, 67u, 67v, 67w, 67x, 67y, 67z, 68a, 68b, 68c, 68d, 68e, 68f, 68g, 68h, 68i, 68j, 68k, 68l, 68m, 68n, 68o, 68p, 68q, 68r, 68s, 68t, 68u, 68v, 68w, 68x, 68y, 68z, 69a, 69b, 69c, 69d, 69e, 69f, 69g, 69h, 69i, 69j, 69k, 69l, 69m, 69n, 69o, 69p, 69q, 69r, 69s, 69t, 69u, 69v, 69w, 69x, 69y, 69z, 70a, 70b, 70c, 70d, 70e, 70f, 70g, 70h, 70i, 70j, 70k, 70l, 70m, 70n, 70o, 70p, 70q, 70r, 70s, 70t, 70u, 70v, 70w, 70x, 70y, 70z, 71a, 71b, 71c, 71d, 71e, 71f, 71g, 71h, 71i, 71j, 71k, 71l, 71m, 71n, 71o, 71p, 71q, 71r, 71s, 71t, 71u, 71v, 71w, 71x, 71y, 71z, 72a, 72b, 72c, 72d, 72e, 72f, 72g, 72h, 72i, 72j, 72k, 72l, 72m, 72n, 72o, 72p, 72q, 72r, 72s, 72t, 72u, 72v, 72w, 72x, 72y, 72z, 73a, 73b, 73c, 73d, 73e, 73f, 73g, 73h, 73i, 73j, 73k, 73l, 73m, 73n, 73o, 73p, 73q, 73r, 73s, 73t, 73u, 73v, 73w, 73x, 73y, 73z, 74a, 74b, 74c, 74d, 74e, 74f, 74g, 74h, 74i, 74j, 74k, 74l, 74m, 74n, 74o, 74p, 74q, 74r, 74s, 74t, 74u, 74v, 74w, 74x, 74y, 74z, 75a, 75b, 75c, 75d, 75e, 75f, 75g, 75h, 75i, 75j, 75k, 75l, 75m, 75n, 75o, 75p, 75q, 75r, 75s, 75t, 75u, 75v, 75w, 75x, 75y, 75z, 76a, 76b, 76c, 76d, 76e, 76f, 76g, 76h, 76i, 76j, 76k, 76l, 76m, 76n, 76o, 76p, 76q, 76r, 76s, 76t, 76u, 76v, 76w, 76x, 76y, 76z, 77a, 77b, 77c, 77d, 77e, 77f, 77g, 77h, 77i, 77j, 77k, 77l, 77m, 77n, 77o, 77p, 77q, 77r, 77s, 77t, 77u, 77v, 77w, 77x, 77y, 77z, 78a, 78b, 78c, 78d, 78e, 78f, 78g, 78h, 78i, 78j, 78k, 78l, 78m, 78n, 78o, 78p, 78q, 78r, 78s, 78t, 78u, 78v, 78w, 78x, 78y, 78z, 79a, 79b, 79c, 79d, 79e, 79f, 79g, 79h, 79i, 79j, 79k, 79l, 79m, 79n, 79o, 79p, 79q, 79r, 79s, 79t, 79u, 79v, 79w, 79x, 79y, 79z, 80a, 80b, 80c, 80d, 80e, 80f, 80g, 80h, 80i, 80j, 80k, 80l, 80m, 80n, 80o, 80p, 80q, 80r, 80s, 80t, 80u, 80v, 80w, 80x, 80y, 80z, 81a, 81b, 81c, 81d, 81e, 81f, 81g, 81h, 81i, 81j, 81k, 81l, 81m, 81n, 81o, 81p, 81q, 81r, 81s, 81t, 81u, 81v, 81w, 81x, 81y, 81z, 82a, 82b, 82c, 82d, 82e, 82f, 82g, 82h, 82i, 82j, 82k, 82l, 82m, 82n, 82o, 82p, 82q, 82r, 82s, 82t, 82u, 82v, 82w, 82x, 82y, 82z, 83a, 83b, 83c, 83d, 83e, 83f, 83g, 83h, 83i, 83j, 83k, 83l, 83m, 83n, 83o, 83p, 83q, 83r, 83s, 83t, 83u, 83v, 83w, 83x, 83y, 83z, 84a, 84b, 84c, 84d, 84e, 84f, 84g, 84h, 84i, 84j, 84k, 84l, 84m, 84n, 84o, 84p, 84q, 84r, 84s, 84t, 84u, 84v, 84w, 84x, 84y, 84z, 85a, 85b, 85c, 85d, 85e, 85f, 85g, 85h, 85i, 85j, 85k, 85l, 85m, 85n, 85o, 85p, 85q, 85r, 85s, 85t, 85u, 85v, 85w, 85x, 85y, 85z, 86a, 86b, 86c, 86d, 86e, 86f, 86g, 86h, 86i, 86j, 86k, 86l, 86m, 86n, 86o, 86p, 86q, 86r, 86s, 86t, 86u, 86v, 86w, 86x, 86y, 86z, 87a, 87b, 87c, 87d, 87e, 87f, 87g, 87h, 87i, 87j, 87k, 87l, 87m, 87n, 87o, 87p, 87q, 87r, 87s, 87t, 87u, 87v, 87w, 87x, 87y, 87z, 88a, 88b, 88c, 88d, 88e, 88f, 88g, 88h, 88i, 88j, 88k, 88l, 88m, 88n, 88o, 88p, 88q, 88r, 88s, 88t, 88u, 88v, 88w, 88x, 88y, 88z, 89a, 89b, 89c, 89d, 89e, 89f, 89g, 89h, 89i, 89j, 89k, 89l, 89m, 89n, 89o, 89p, 89q, 89r, 89s, 89t, 89u, 89v, 89w, 89x, 89y, 89z, 90a, 90b, 90c, 90d, 90e, 90f, 90g, 90h, 90i, 90j, 90k, 90l, 90m, 90n, 90o, 90p, 90q, 90r, 90s, 90t, 90u, 90v, 90w, 90x, 90y, 90z, 91a, 91b, 91c, 91d, 91e, 91f, 91g, 91h, 91i, 91j, 91k, 91l, 91m, 91n, 91o, 91p, 91q, 91r, 91s, 91t, 91u, 91v, 91w, 91x, 91y, 91z, 92a, 92b, 92c, 92d, 92e, 92f, 92g, 92h, 92i, 92j, 92k, 92l, 92m, 92n, 92o, 92p, 92q, 92r, 92s, 92t, 92u, 92v, 92w, 92x, 92y, 92z, 93a, 93b, 93c, 93d, 93e, 93f, 93g, 93h, 93i, 93j, 93k, 93l, 93m, 93n, 93o, 93p, 93q, 93r, 93s, 93t, 93u, 93v, 93w, 93x, 93y, 93z, 94a, 94b, 94c, 94d, 94e, 94f, 94g, 94h, 94i, 94j, 94k, 94l, 94m, 94n, 94o, 94p, 94q, 94r, 94s, 94t, 94u, 94v, 94w, 94x, 94y, 94z, 95a, 95b, 95c, 95d, 95e, 95f, 95g, 95h, 95i, 95j, 95k, 95l, 95m, 95n, 95o, 95p, 95q, 95r, 95s, 95t, 95u, 95v, 95w, 95x, 95y, 95z, 96a, 96b, 96c, 96d, 96e, 96f, 96g, 96h, 96i, 96j, 96k, 96l, 96m, 96n, 96o, 96p, 96q, 96r, 96s, 96t, 96u, 96v, 96w, 96x, 96y, 96z, 97a, 97b, 97c, 97d, 97e, 97f, 97g, 97h, 97i, 97j, 97k, 97l, 97m, 97n, 97o, 97p, 97q, 97r, 97s, 97t, 97u, 97v, 97w, 97x, 97y, 97z, 98a, 98b, 98c, 98d, 98e, 98f, 98g, 98h, 98i, 98j, 98k, 98l, 98m, 98n, 98o, 98p, 98q, 98r, 98s, 98t, 98u, 98v, 98w, 98x, 98y, 98z, 99a, 99b, 99c, 99d, 99e, 99f, 99g, 99h, 99i, 99j, 99k, 99l, 99m, 99n, 99o, 99p, 99q, 99r, 99s, 99t, 99u, 99v, 99w, 99x, 99y, 99z, 100a, 100b, 100c, 100d, 100e, 100f, 100g, 100h, 100i, 100j, 100k, 100l, 100m, 100n, 100o, 100p, 100q, 100r, 100s, 100t, 100u, 100v, 100w, 100x, 100y, 100z.

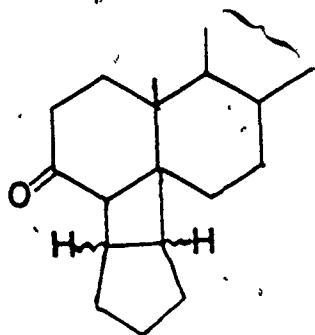
trans-fused products.

## 2.6 Photocycloaddition of testosterone propionate (15a) to cyclopentene

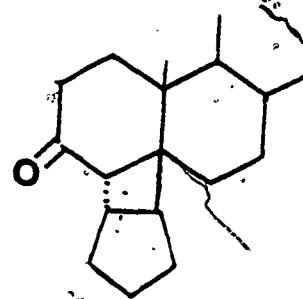
Photocycloaddition of 15a to cyclopentene both on silica gel and in solution gave the known<sup>63</sup> 4 $\alpha$ ,5 $\alpha$  and 4 $\alpha$ ,5 $\beta$  isomers (17a and 17c) together with the previously unreported 4 $\beta$ ,5 $\beta$  isomer (17b). The crude irradiation product was purified by flash chromatography to give the reported 17a which was identified as the cyclobutane adduct by the presence of a carbonyl absorption in the I.R. spectrum at 1680 cm<sup>-1</sup>. The stereochemistry at the ring junction was assigned as cis-4 $\alpha$ ,5 $\alpha$  on the basis of the (+Ve) Cotton effect in the (CD) spectrum. The second isomer (17c) possessed a trans 6/4 ring junction. The stereochemistry at the ring junction was assigned as 4 $\alpha$ ,5 $\beta$  on the basis of the (+Ve) Cotton effect in the CD spectrum. An examination of a Drieding model of trans-4 $\alpha$ ,5 $\beta$  isomer (17c) indicated that it can only be constructed with ring B in the boat form and ring A in a severely constrained chair conformation. The resulting model was almost completely rigid and involved considerable strain. An octant projection of this model correctly predicted the strong, positive Cotton effect in the CD spectrum, as was observed. The smaller Cotton effect observed in 4 $\alpha$ ,5 $\alpha$  cycloadduct (17a) indicated that ring A in (17a) could assume a chair or boat conformation. Examination of both



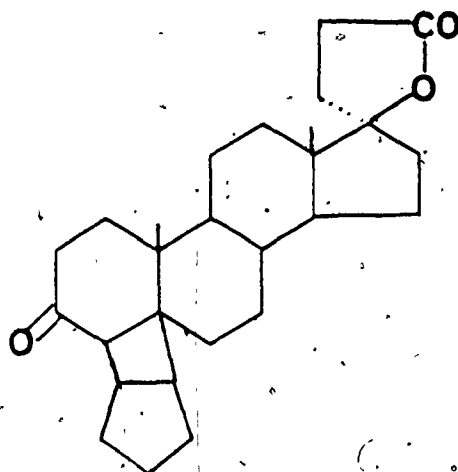
17a



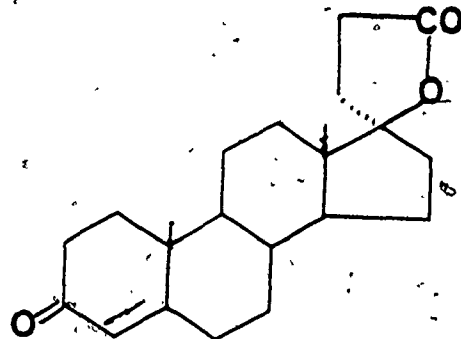
17b, 17d



17c

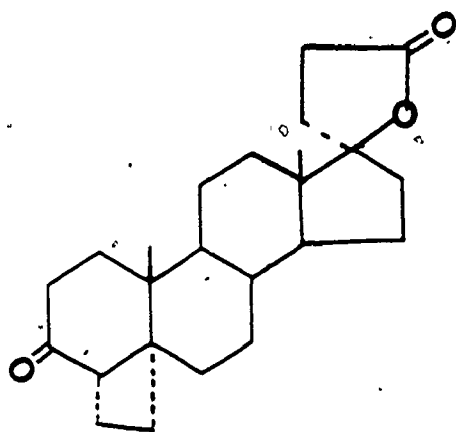


20

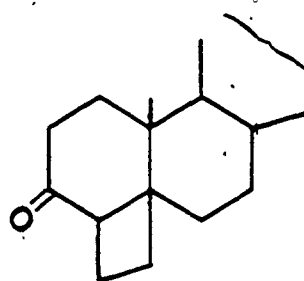


21





22a



22b

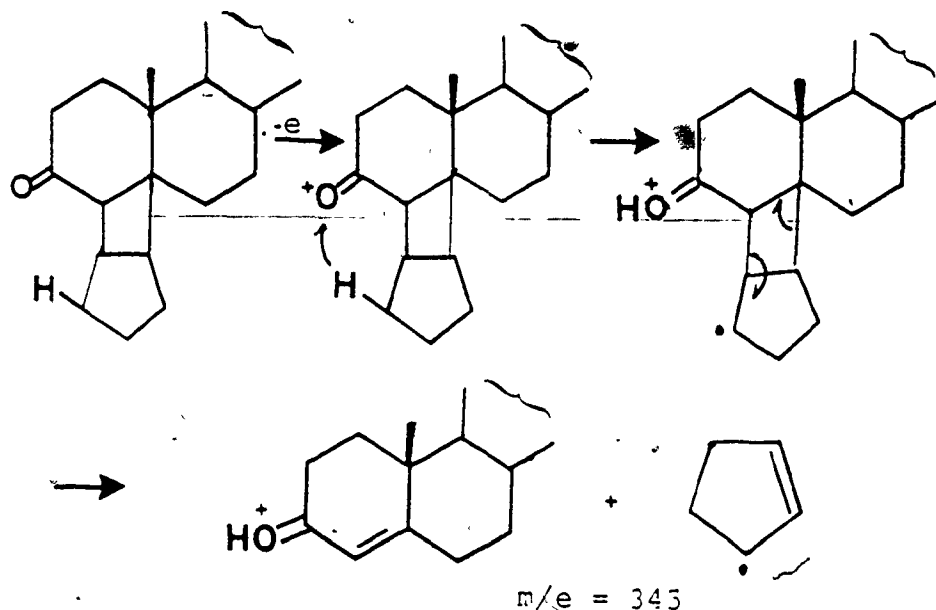
the possibilities in (17a) on an octant diagram predicted weaker Cotton effect than 17c, as was observed.

The third isomer off the column 17b was identified as a cyclobutane adduct by the presence of a carbonyl absorption at  $1680\text{ cm}^{-1}$  in the I.R. spectrum. The stereochemistry at the ring junction was assigned as  $4\beta,5\beta$ , based on the -Ve sign of the Cotton effect in the CD spectrum. As previously reported,<sup>63</sup> the trans isomer was isomerised on heating to 17d, a further cis-isomer. From R<sub>f</sub> on tlc, retention time on g.l.c. and m.p. the two cis  $\beta$  isomers, 17b and 17d, were clearly different.

They were both assigned the cis  $4\beta,5\beta$  stereochemistry based on the signs and magnitude of the Cotton effect in the circular dichroism spectra: 17b  $[\theta]_{294} = -6511$ ; 17d  $[\theta]_{299} = -7772$  (lit<sup>63</sup> -6639) and by analogy with 20 ( $[\theta]^{64} = -4900$ ). Presumably the two isomers are cis-syn-cis and cis-anti-cis, but none of the spectral techniques available to us enabled a decision to be made as to allocation of stereochemistry. The following unsuccessful attempts were made in arriving at the stereochemistry of 17b and 17d. Firstly, it was reasoned that the syn isomer being more hindered than the anti isomer, the resulting proximity of the cyclopentyl ring to the angular methyl group in the former isomer would lead to a hindering of the free rotation of this angular methyl group. Therefore it was thought that at low temperature the signal due to the methyl group might broaden, at least, in the syn isomer.

However the  $^1\text{Hmr}$  spectrum for both isomers did not show any change even at  $-100^\circ\text{C}$ .

Secondly, in the mass spectrum of isomeric adducts a strong peak was



Scheme XII

observed at  $m/e = 345$ , which is attributed to the loss of cyclopentenyl radical (Scheme XII). It was thought that the intensity of the base peak ( $m/e = 345$ ) might give an indication of the stereochemistry in these adducts (17b and 17d). However, the mass spectrum even at 25 ev failed to distinguish between these two isomeric adducts.

These results contrast with those of Lehz in the addition of cyclopentene to 21.<sup>64</sup> This reaction yielded the  $4\alpha,5\alpha$  and  $4\alpha,5\beta$  isomers, together with ~10% of the  $4\beta,5\beta$  (20) product; however, on heating, the trans isomer yielded the photochemically obtained  $4\beta,5\beta$  adduct, in contrast with our results wherein the photochemically

obtained  $\text{cis } \beta$  17b and thermally isomerized  $\text{cis } \beta$  17d are different compounds.

Comparison of the relative amounts of  $\alpha$  versus  $\beta$  attacks in methanol and on silica gel is rendered difficult by the presence of a major amount of the ambiguous trans isomer formed in methanolic solution at room temperature. Methanol and silica gel may be better compared at  $-78^\circ\text{C}$ , where similar (and smaller) amounts of trans-isomer are present: again, the product ratio shifts in favour of  $\beta$  approach by a factor of 2.

## 2.7 Photocycloaddition of testosterone propionate (15a) to allene

One method of avoiding the stereochemical ambiguity in mode of approach introduced by the formation of trans-fused products (it has not yet been decisively shown whether the  $\alpha$  or  $\beta$  bond from the enone is formed first in the products),<sup>72</sup> is to use an addend where strain precludes their formation. Such is the case with allenes.

Photocycloaddition of 15a to allene in methanol solution resulted in preferential reaction from the  $\alpha$  side in a ratio of 5:1 at room temperature increasing to 9:1 at  $-78^\circ\text{C}$ . In contrast, on silica gel  $\beta$  products were slightly favoured and the ratios were essentially temperature independent: from methanol to silica gel the ratio changed by about one order of magnitude.

These adducts were characterised as follows. The

separation of the product from the silica gel reaction gave 18c in 6% yield, based on the initial starting material. The cycloadducts were well separated on tlc, but adducts 18b and 18c were not resolved by g.l.c. The cis  $\alpha$  and  $\beta$  adducts, 18a and 18b showed low field proton-signals in the  $^1\text{Hmr}$  spectrum at  $\delta$  3.06 and 3.13, respectively, attributed to the methine proton at C-4: an indication of head to head (HH) regiochemistry. This was also substantiated by the medium intensity ultraviolet maximum at 293 nm ( $\epsilon = 187$ ), characteristic of a  $\beta\gamma$  unsaturated ketone. In contrast, 18c showed a very weak UV absorption maximum at 283 nm ( $\epsilon = 31$ ), characteristic of an unperturbed carbonyl group, and no low field signal was detected near 3.0 ppm, both features indicating a head to tail (HT) regiochemistry.

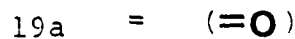
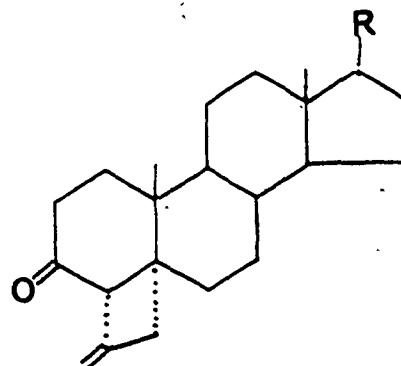
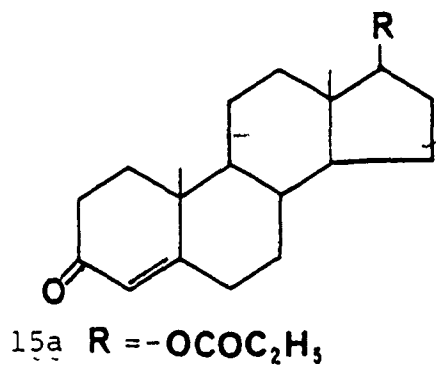


TABLE 2.2 <sup>a</sup>CIRCULAR DICHROISM OF STEREOISOMERIC 3-KETO-4-  
ENE-STEROID ADDUCTS

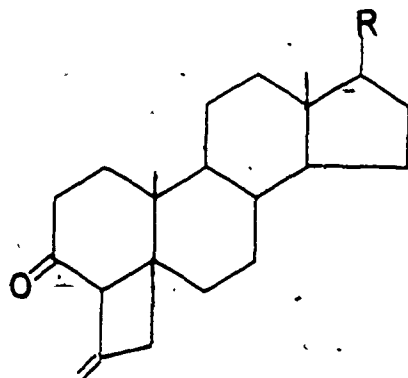
Ketone	$\lambda_{\text{max}}(\text{nm})$	$\theta^\circ$
<u>Adducts of the 4<math>\alpha</math>,5<math>\alpha</math> series</u>		
16a	290	+1967 <sup>b</sup>
22a	289	+2100 <sup>b</sup>
18a	292	+2128
17a	292	+7030
<u>Adducts of the 4<math>\beta</math>,5<math>\beta</math> series</u>		
22b	291	-3050 <sup>b</sup>
16b	290	-3278 <sup>b</sup>
18b	292	-2523
18c	284	-1256
17b	294	-6511
17d	299	-7772
20	291	-4900 <sup>c</sup>

<sup>a</sup>Solvent: CH<sub>3</sub>OH

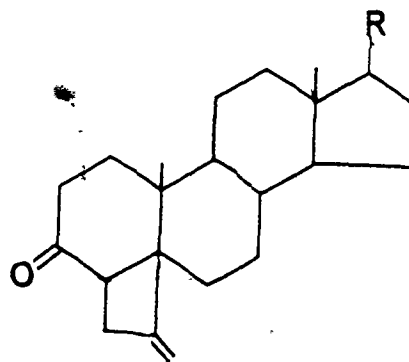
<sup>b</sup>from reference 63

<sup>c</sup>from reference 64

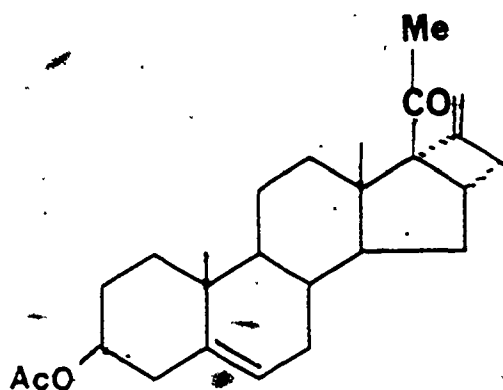
The correct precise masses were obtained for the isomeric adducts 18a-18c. The stereochemistry at the ring junction was assigned from the sign of the Cotton effect in the CD spectra of the isomeric adducts: an examination of Drieding models for isomeric octant diagrams suggested that the sign should be negative for 18b and 18c and positive for the  $\alpha$ -cis adduct 18a. The stereochemical assignment, i.e.  $4\alpha,5\alpha$  and  $4\beta,5\beta$ , draws analogy from that reported in literature for  $\beta\gamma$  unsaturated ketones and for ethylene-enone adducts (Table 2.2).<sup>63-65</sup> The large Cotton effect observed in the case of  $\beta\gamma$  unsaturated ketone adduct 18b as compared to  $\gamma\delta$  adduct 18c draws analogy with that reported by Fried for 23a and 23b.<sup>65</sup>



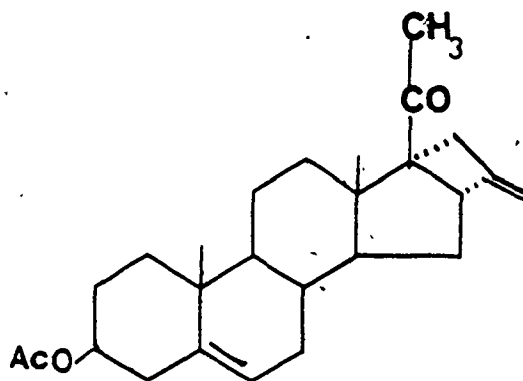
18b R =  $-\text{OCC}_2\text{H}_5$   
 19b =  $(=\text{O})$



18c R =  $-\text{OCC}_2\text{H}_5$   
 19c =  $(=\text{O})$


 $[\alpha]_{295} -18,180$ 

23a


 $[\alpha]_{295} 5780$ 

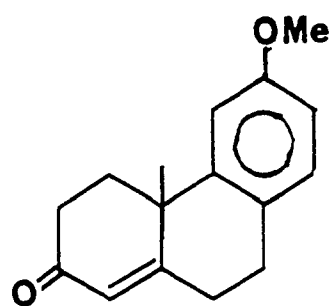
23b

In this study alumina was also used as the adsorbent. The preference for the  $\beta$  face products in the photocycloaddition of 15a to allene on alumina was even stronger than on silica gel, and, in fact, the photocycloaddition of allene to 15a and 15c on alumina, lead to complete reversal of stereochemistry to that observed in methanolic solution, see Table 2.1.

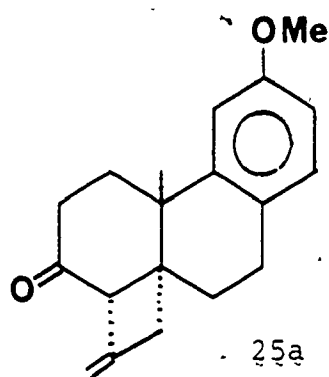
The preferential formation of  $\beta$  adducts on silica and alumina surface contradicts the prediction made on the basis of Wiesner's proposal. Since allene addition always results in the formation of cis-fused adduct, one cannot, from the stereochemistry, discuss whether  $\alpha$  or  $\beta$  bond formation occurred first.<sup>49</sup> Evidence is available, that, the initial bond formation can be at  $C_\alpha$  or  $C_\beta$ ,<sup>72</sup> depending upon the structures of alkene and enone involved.

According to Wiesner's rule,<sup>70</sup> an overlap of the enone  $\beta$

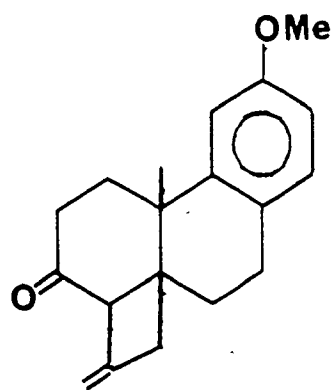




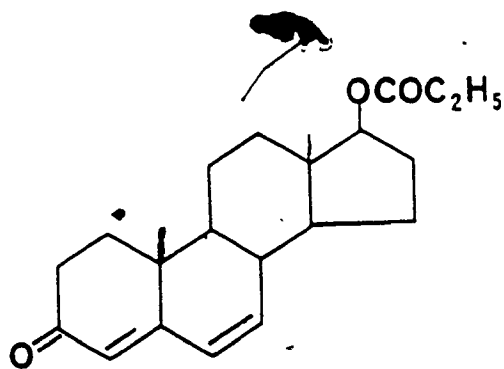
24



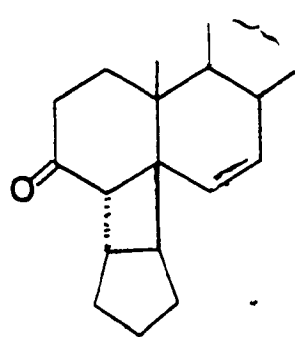
25a



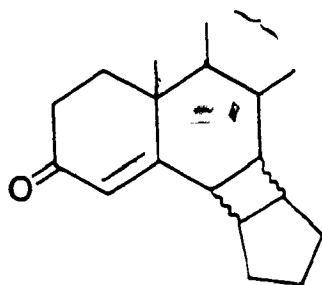
25b



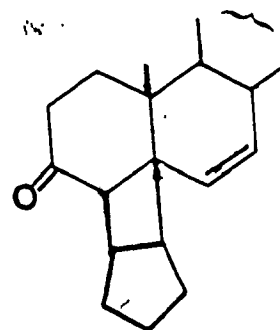
26



27a



27b



27c

orbital with a terminal orbital of allene would be required. To the extent that analogy with carbon centred radicals is any guide, enone addition to the terminal position of the allene should occur<sup>74</sup> (see Chapter 3). Since the attack at the terminal position is probably unaffected by the adsorption on silica gel the formation of a  $\gamma\delta$  regioisomeric adduct is an indication of, under these conditions and in these products, at least, first bond formation at the  $\alpha$  (not the  $\beta$ ) position of the steroidal enone, which contradicts Wiesner's proposal.

## 2.8 Photocycloaddition of testosterone and epi-- testosterone to allene

The most effective binding site ~~is~~ the enone chromophore is the carbonyl oxygen. Only secondary forces require the molecule to lie 'flat' on the gel surface, and it is on these forces that the effective protection of one face of the molecule depends since, otherwise the steroid might take up a position orthogonal to the 'plane' of the gel. Secondary binding sites must, therefore, be important. The photocycloaddition of 15b and 15c to allene was investigated in order to compare the extent of interaction of steroidal enones having equatorial ( $\beta$ ) and axial ( $\alpha$ ) alcoholic function at C<sub>17</sub>, respectively, with the surface silanols. With 15b the extent of attack on the  $\beta$  face in solution and on silica was comparable to that found with the corresponding propionylated steroid 15a. This was

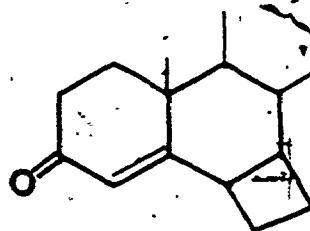
not surprising since the oxygen function is on the face away from the gel. However, the epimeric alcohol, 17-epitestosterone (15c), also did not produce, on silica gel, any very striking change as compared with the 17 $\beta$ -propionate. The results on alumina, however, showed signs of the expected stronger binding. The irradiation of 15c and allene on alumina resulted in the complete reversal of stereochemistry to that observed in methanolic solution. Such a change in composition can be synthetically useful. The testosterone and epitestosterone allene adducts were oxidized, to eliminate stereochemistry at C-17, to obtain the corresponding testosterone-dione adducts (19a - 19c), the stereochemistry of which has been already established by us. These results indicate that, irrespective of the 17-substituent, the molecule is lying, at least partly, flat, and cumulative secondary forces must be important in a large molecule such as steroid.

An irradiation of 15b and allene was carried out in acidified methanolic solution (HCl, pH 3) to ensure that our observed results were not merely a function of the silanol acidity. No difference from the behaviour in methanolic solution was observed.

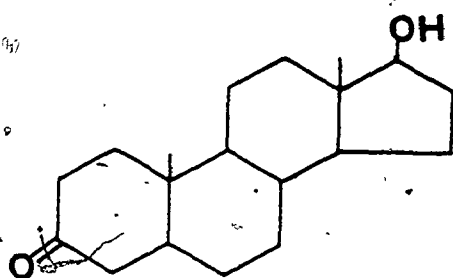
## 2.9 Photocycloaddition of 12-methoxy-18,19--

bisnorpodocarpa-4,8,11,13-tetrene-3-one) (24) to allene

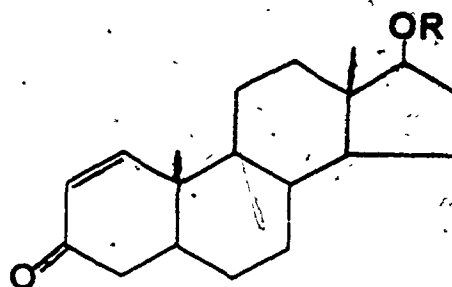
Although not a steroid, the addition of allene to 24 (12-methoxy-18,19-bisnorpodocarpa-4,8,11,13-tetren-3-one)



28



29



30a R = H

30b R = -COCH<sub>3</sub>

was briefly studied, to see the effect of a single steric centre. In methanolic solution and on silica gel two adducts 25a and 25b were obtained. The stereochemistry was tentatively arrived at by analogy with 15a. The major product 25a was recrystallized from methanol to give a melting point of 70-72°C. The I.R. spectrum revealed absorption at  $1690\text{ cm}^{-1}$  for 25a and 25b representing carbonyl absorption. In the  $^1\text{Hmr}$  spectrum of 25a and 25b two olefinic protons were represented by a multiplet at  $\delta$  5.0. The difference in product composition found between methanol at -70°C and silica gel was small, but indicated a shift towards  $\beta$  face addition. The compound 24 was not stable on the alumina surface and so the irradiation on an activated alumina surface was not performed.

#### 2.10 Photocycloaddition of $\Delta^{4,6}$ -androstadien-3-one-17 $\beta$ -ol-propionate (26) to cyclopentene

$\Delta^{4,6}$ -Androstadien-3-one-17 $\beta$ -ol-propionate 26 was prepared by the oxidation of testosterone propionate 15a with chloranil.<sup>75</sup> The  $^1\text{Hmr}$  spectrum displayed a singlet at  $\delta$  6.05 representing the olefinic protons at C<sub>6</sub> and C<sub>7</sub>. The proton at C<sub>4</sub> appeared as a singlet at  $\delta$  5.75 in the  $^1\text{Hmr}$  spectrum. The mass spectrum contained the expected molecular ion at 342 mass units.

The photocycloaddition of cyclopentene to  $\Delta^{4,6}$ -androstadien-3-one-17 $\beta$ -ol-propionate (26) has been reported<sup>63</sup> to give 27a in 82.3 % yield. On silica gel this

remained the major product, but 28% attack, to give 27b, was also found. The structure of the 6,7 cycloadduct 27b followed from the UV spectra ( $\lambda_{\text{max}}$ (MeOH) 255 nm,  $\epsilon$  12,000),  $^1\text{Hmr}$  ( $\delta$  5.7, brs, 1H), IR (1655, 1720  $\text{cm}^{-1}$ ) and mass spectrum (molecular ion 410 mass units): no attempt was made to determine the stereochemistry at the ring junction. The structural assignment draws analogy from that reported for 28, ( $\lambda_{\text{max}}$ (EtOH) 250 nm,  $\epsilon$  14,700),  $^1\text{Hmr}$  ( $\delta$  5.67, s, 1H) indicating the presence of the testosterone moiety.<sup>76</sup> The reported trans isomer 27a was assigned as the 4,5 cyclopentene cycloadduct, as evidenced by the coupling of protons at C<sub>6</sub>, C<sub>7</sub> and C<sub>9</sub>. These protons formed an ABX pattern with coupling constants of -10 and -2 Hz. The trans stereochemistry allocated was further supported by the ready epimerization of 27a with base to give the more stable cis-fused cycloadduct 27c. The melting point was found identical with that reported in the literature. In addition to 27b, 5.5% of an unidentified cycloadduct was also obtained. In all the isomeric adducts a mass ion ( $M^+$  410) corresponding to the addition of one molecule of cyclopentene to an enone molecule 26 was obtained in the mass spectrum. The increased addition at the  $\gamma\delta$  position is consonant with the view that the primary binding is at the carbonyl function, and hence that end of the chromophore is closest to the silica gel surface, thus leaving the 6,7 bond relatively exposed.

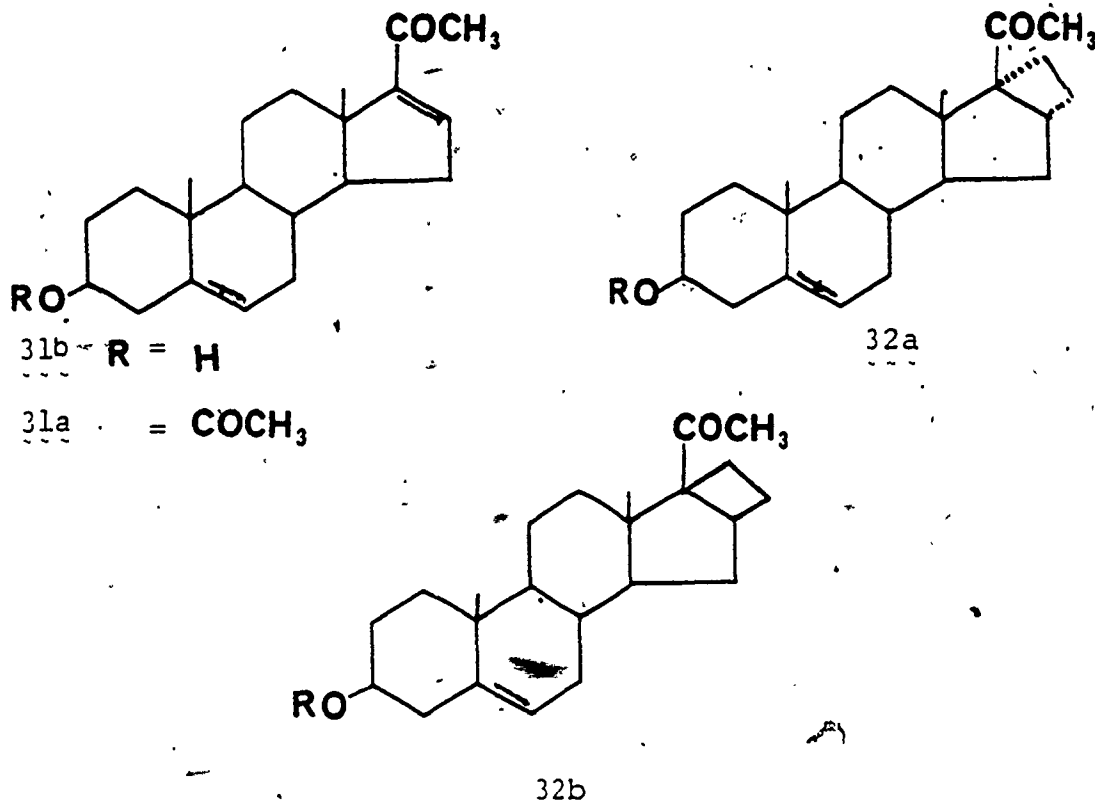
## 2.11 Photocycloaddition of 17 $\beta$ -acetoxy-5 $\alpha$ -androst-1-en-3-one (30b) to cyclopentene

17 $\beta$ -Hydroxy-5 $\alpha$ -androst-1-en-3-one (30a) was prepared by dehydrogenation of androstanolone, 29 with (DDQ). Its acetylation with acetic anhydride and pyridine gave 30b.<sup>77</sup> The <sup>1</sup>Hmr spectrum displayed doublets at  $\delta$  7.2 ( $J = 10\text{Hz}$ ) and  $\delta$  5.9 ( $J=10\text{Hz}$ ) representing olefinic protons at C<sub>1</sub> and C<sub>2</sub>. The I.R. spectrum showed absorption at 1665 cm<sup>-1</sup> representing the carbonyl of the enone function. The correct precise mass was obtained. The irradiation of 30b and cyclopentene in ethyl acetate was performed by the procedure of Lenz.<sup>78</sup> Analysis of the product mixture showed the presence of a compound less polar than the starting material 30b. In comparison to solution irradiation the photocycloaddition of 30b to cyclopentene on silica gel was very slow. G.C. analysis indicated ~10% conversion in 30 hr of irradiation. The mass spectrum of the crude irradiation product indicated the addition of cyclopentene to enone 30b. Since the reaction on the silica gel surface was very slow, further detailed analysis was not pursued.

## 2.12 Photocycloaddition of 3 $\beta$ -acetoxypregna-5,16-dien-20-one (31a) and 3 $\beta$ -hydroxypregna-5,16-dien-20-one (31b) to ethylene

The final study was an endeavour to determine whether rigidity of the enone function was necessary for the effect

of silica gel to be manifested. For this purpose the 20-ketone 31a and 31b were employed.



The photocycloaddition of 31a to ethylene in benzene solution was carried out by the procedure of Sunder-Plassman et al.<sup>65</sup> to give the 16 $\alpha$ ,17 $\alpha$  (32a) and 16 $\beta$ ,17 $\beta$  (32b) isomers. In methanolic solution  $\alpha$  addition was favoured by 19:1, whereas on silica gel a shift towards  $\beta$  face addition was observed. The crude silica irradiation product was chromatographed to give 16 $\alpha$ ,17 $\alpha$  (32a) isomer, which was identified as the cis fused cyclobutane adduct by the presence of a carbonyl absorption at 1690 cm<sup>-1</sup> in the I.R. spectrum. The <sup>1</sup>Hmr of these compounds exhibited two singlets at  $\delta$  0.6 and 2.0, integrating for 3 protons each, which were attributed to the C-18 angular methyl and acetyl



respectively. The second isomer 16 $\beta$ 17 $\beta$  (32b) was also assigned cis-stereochemistry by the presence of an unconjugated carbonyl absorption at 1690  $\text{cm}^{-1}$  in the I.R. spectrum.  $^1\text{Hmr}$  spectrum of this adduct showed two singlets at 1.16 and 2.0 ppm, integrating for 3 protons each, which were assigned to the C-18 angular and acetyl ( $\text{CH}_3-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$ ) methyl groups respectively. The deshielding experienced by the C-18 methyl of 32b is attributed to the anisotropy of the  $\beta$ -oriented cyclobutane ring. It is analogous to 28, where the cyclobutane ring also caused a -1.3 ppm downfield shift of the C-19 methyl.<sup>76</sup>

The photocycloaddition of 31b to ethylene in benzene solution and on silica was comparable to that obtained with the corresponding acetylated steroid. This was not unexpected since the alcoholic function is on the face away from the gel. The irradiation mixtures obtained were acetylated and the products were analysed by G.C. The steroids 31a and 31b were not stable on activated alumina surface. After desorption, G.C. analysis and tlc showed the formation of unidentified products. These by-products must be derived from the reaction of the reactive acetyl functionality in these two steroids with the alumina surface.

## 2.13 CONCLUSION

These studies described above demonstrate that the steric course of steroid enone photocycloaddition can be

modified by prior adsorption of the steroid on silica gel and alumina. Results are consistent with the view that the adsorption takes place on the gel from the less hindered face ( $\alpha$ ) leaving the  $\beta$  face more available for reaction. It appears likely that adsorption on the surface disfavours conformational inversion in the intermediate 1,4 biradical which is required for trans addition to occur.

## CHAPTER 3

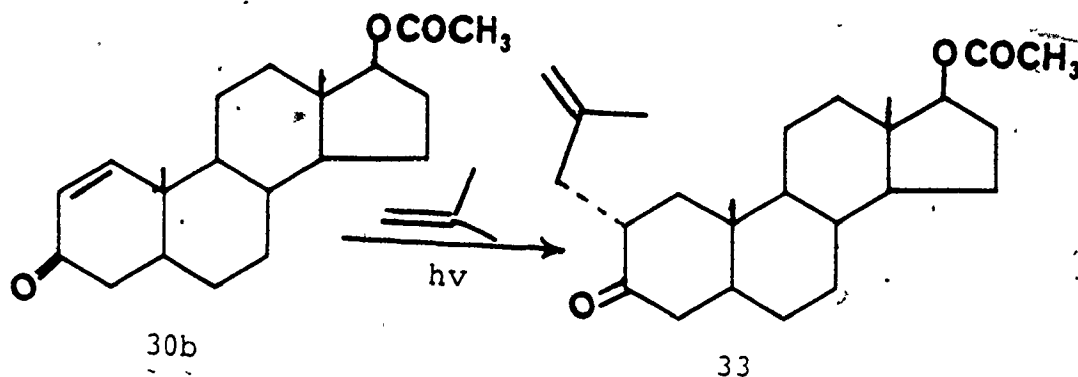
### MORE ON THE STEREOCHEMISTRY OF ENONE PHOTOCYCLOADDITION

#### 3.1 INTRODUCTION

##### 3.1.1 Wiesner's Proposal

Some years ago, Wiesner proposed<sup>70</sup> that the stereochemistry of the enone photocycloaddition could be predicted from the conformational posture of the enone excited state. It was postulated that the configuration of the photoadduct is controlled by a species which is trigonal in the  $\alpha$ - and pyramidal in the  $\beta$  position. This species was assumed to select the more stable configuration and thus to determine the configuration of the adduct: this resultant stereochemistry might or might not derive from the steric ease of approach of the olefin. According to the proposal the  $\alpha$  carbon is slightly positive in comparison to the  $\beta$  carbon in the transition state and an overlap of the  $\beta$  orbital with the terminal position of allene would be required for bond formation. Since allene addition always results in the formation of a cis-fused adduct, one cannot, on stereochemical grounds predict whether  $\alpha$  or  $\beta$  bond formation occurred first.<sup>49</sup> The question of whether the biradical intermediate is formed by the initial bond formation at  $C_\alpha$  or  $C_\beta$  is not well resolved,<sup>48</sup> although there is evidence that the initial bond formation can, in fact, be at the  $C_\alpha$  or  $C_\beta$  position of the enone depending upon the structure of the enone and alkene involved, as discussed below.

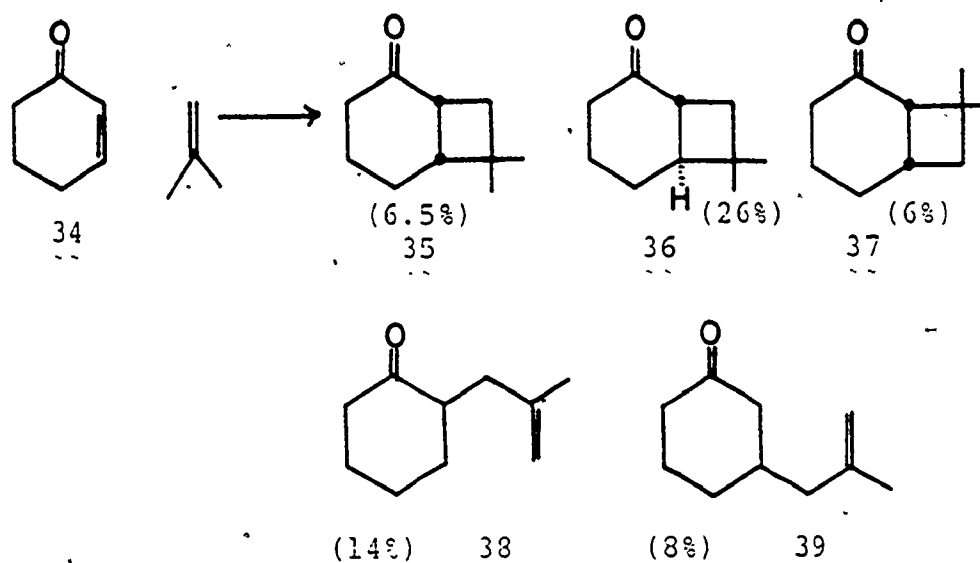
### 3.1.2 Evidence for Initial Bond Formation at $\alpha$ -Carbon and $\beta$ -Carbon of Enones



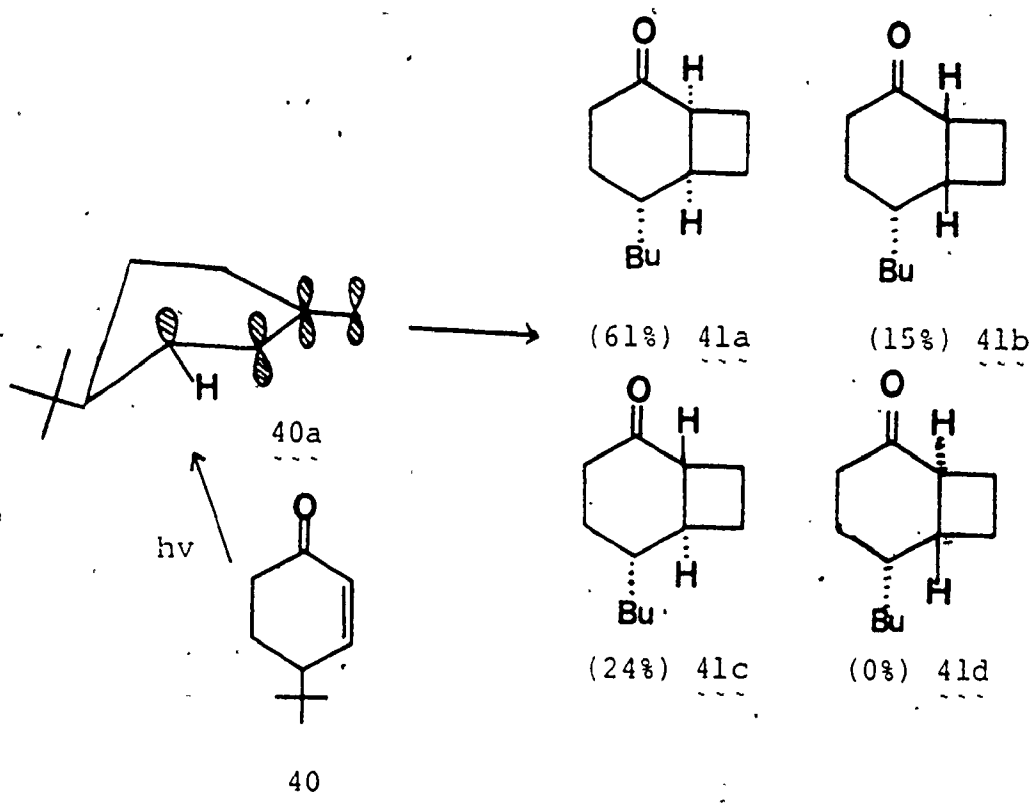
Scheme XIII

In the case of photocycloaddition of 17 $\beta$ -acetoxy-5 $\alpha$ -androst-1-en-3-one (30b) to isobutylene the olefinic by-product 33 indicated that the initial bond formation was at C $\alpha$  carbon (Scheme XIII).<sup>45</sup> In contrast, intramolecular photocycloaddition of enones to allene is more easily analyzed by assuming the initial bonding at the  $\beta$  position of the enone.<sup>72c</sup>

The frequent observation of olefinic products derived from an initial bonding at  $\alpha$  and  $\beta$  carbon in an enone photocycloaddition reaction indicates that the initial bonding can occur at both positions depending upon the structure of the enone and olefin involved. In the photocycloaddition of iso-butylene to cyclohexenone (34) the olefinic products 38 and 39 indicate that the initial bonding is at C $\alpha$  and C $\beta$ .<sup>79</sup>



Scheme XIV



Scheme XV

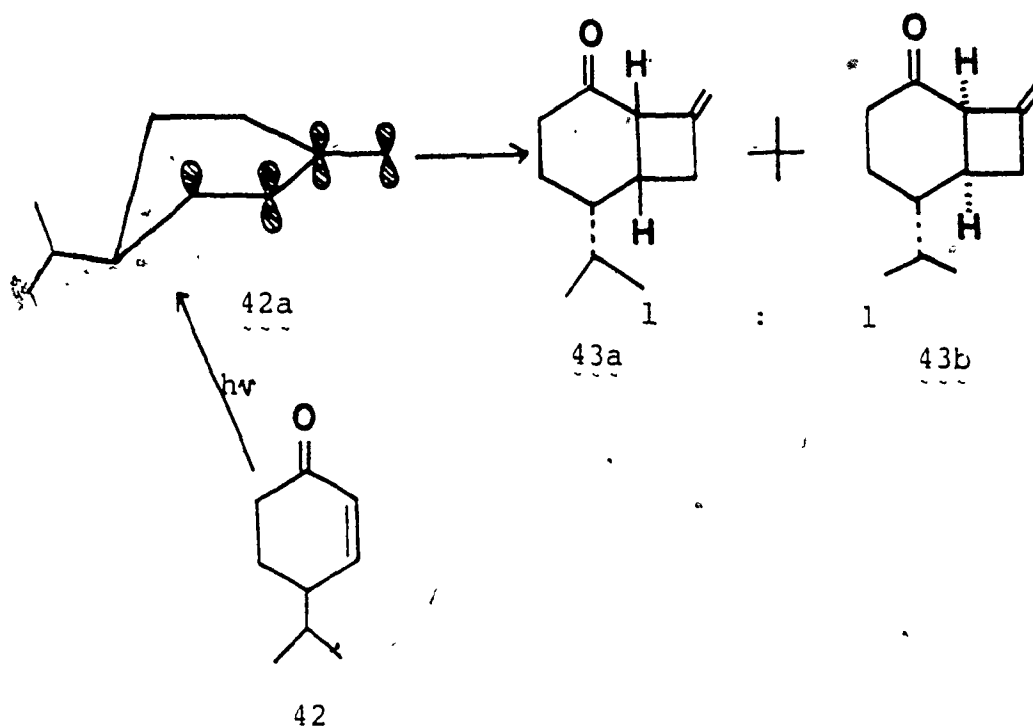
### 3.1.3 Exception to the Wiesner Rule in Homogeneous Systems

In an attempt to test the Wiesner's empirical rule, Cargill has performed the photocycloaddition of 4t-butylcyclohexenone (40) with ethylene and obtained the cycloadducts 41a-41c.<sup>80</sup> According to Wiesner's empirical proposal, the enone 40 would be expected to react with ethylene from the conformational posture 40a to give a cis adduct 41b or perhaps the trans-fused adduct 41d. If the attack of ethylene occurs from the less hindered side of enone 40, the reaction should lead to cis-fused adduct 41a and trans-adduct 41c as the major photoproducts. Product analysis indicated that attack of ethylene did indeed occur from the less hindered side of enone 40 to give 41a and 41c (see Scheme XV).

Wiesner also pointed<sup>81</sup> out an exception to his proposal in the photocycloaddition of isopropyl cyclohexenone (42) to allene and obtained an equal amount of 43a and 43b. According to Wiesner's empirical rule, the enone 42 would be expected to react from configuration 42a to give 43a (see Scheme XVI).

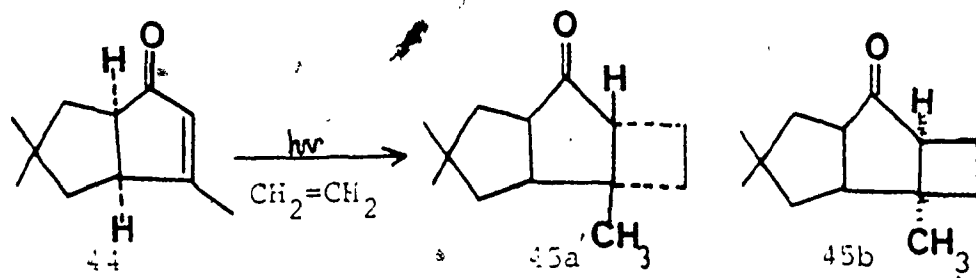
Recently, an exception to Wiesner's proposal has been also reported in the photocycloaddition of  $\Delta^{4,5}$ cholesten-3-one to acetylene where it gave 4 $\alpha$ ,5 $\alpha$  adduct and 4 $\beta$ ,5 $\beta$  adduct (see Chapter II, Scheme XI). According to Wiesner's proposal 4 $\alpha$ ,5 $\alpha$  adduct would be predicted as the sole

product.

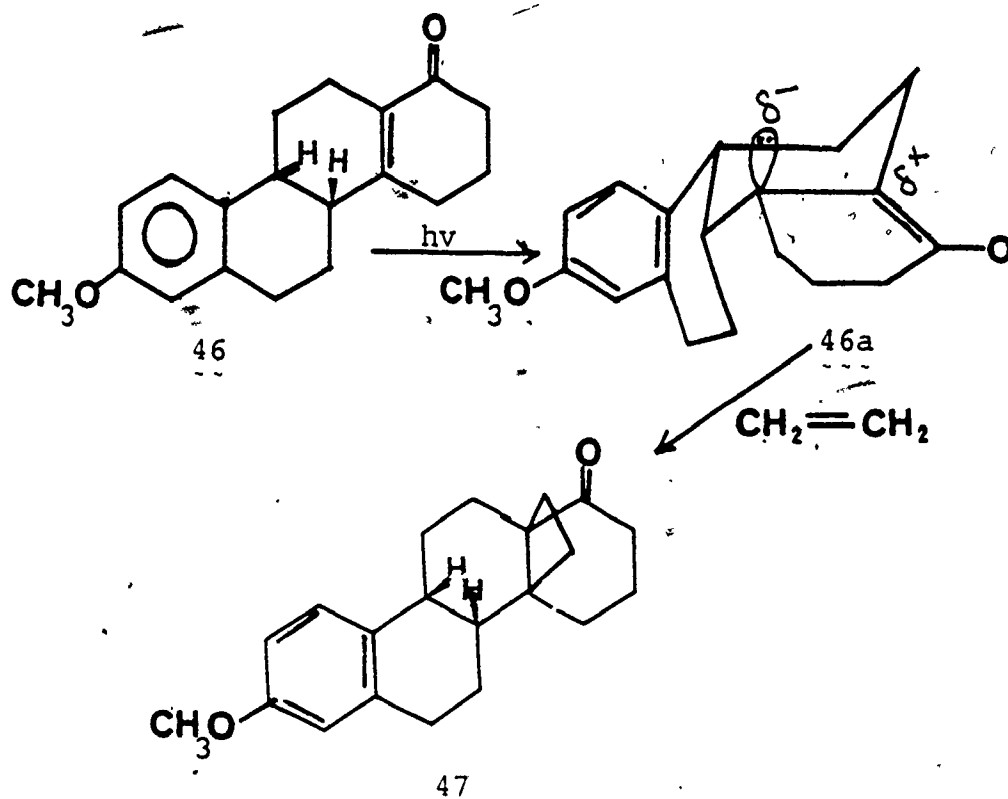


## SCHEME XVI

The photocycloaddition of 44 with ethylene gave 45a as a major photoproduct, the formation of which also contradicts Wiesners proposal.<sup>82</sup>



## SCHEME XVI-I



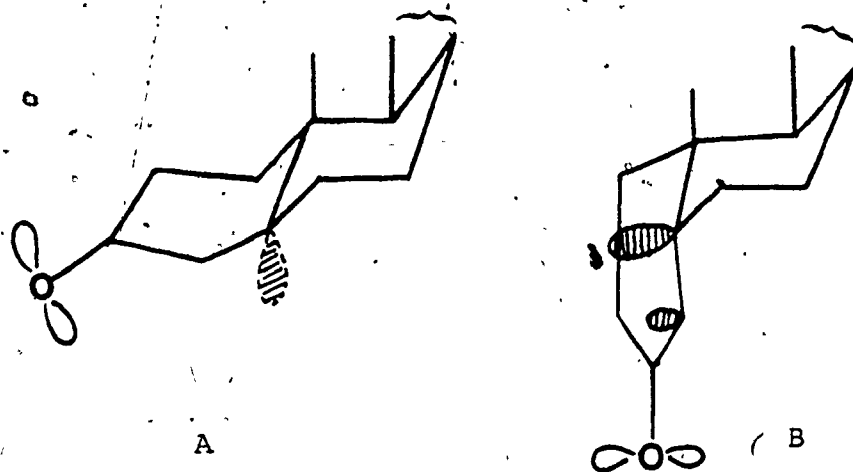
#### SCHEME XVIII

Cargill reported<sup>83</sup> that photocycloaddition of ethylene to 46 gave only 47. The formation of 47 as the sole product of photocycloaddition was rationalized in terms of Wiesner's model and intermediate 46a. Baldwin later pointed out<sup>47</sup> that this result was not an adequate test of Wiesner's empirical rule, because steric ease of approach would also predict the same result.

#### 3.1.4 Exceptions to Wiesner's Proposal in Heterogeneous Systems

As already described in chapter II the formation of the  $\beta$  products on silica and alumina surface contradict the predictions made on the basis of Wiesner's empirical rule.





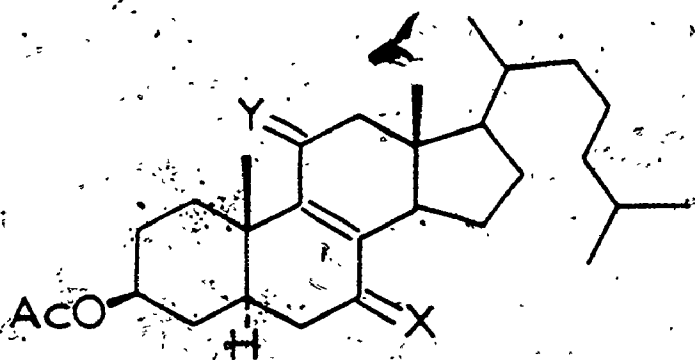
According to Wiesner's rule 3-keto-4-ene steroid would be expected to react from the configuration A to give 4 $\alpha$ ,5 $\alpha$  adducts. This conformational posture was selected over B based on the analysis of non bonding interactions. The steric ease of approach by olefin would also predict the formation of 4 $\alpha$ ,5 $\alpha$  adduct. The formation of the more hindered face ( $\beta$ ) adduct on silica and alumina suggested that the reaction occurs via configuration B (which was rejected on the basis of nonbonding interactions).

The formation of  $\beta$ -face products in the case of those steroidal enones whose  $\beta$ -face is more open to attack than the  $\alpha$ -face when adsorbed on the gel clearly indicates that the steric ease of approach is the deciding factor in the photocycloaddition reaction.

### 3.1.5 Choice of Substrates

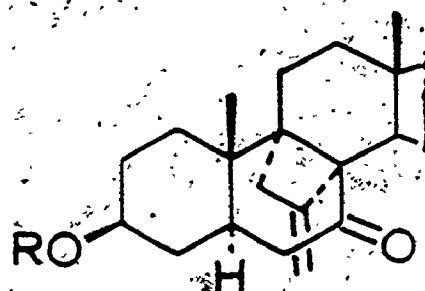
Wiesner carried out the photocycloaddition of structurally similar steroids 48a and 48b with allene at

-78°C, as a test case to his rule.<sup>71</sup> It was expected<sup>71</sup> that 48a should undergo reaction on the  $\alpha$ -face, and it, indeed, did so giving 49a (together with 50). On the other hand 48b was predicted to react from the  $\beta$  face, but the reaction could be inhibited by steric hindrance: in fact, the reaction was found to be very sluggish.



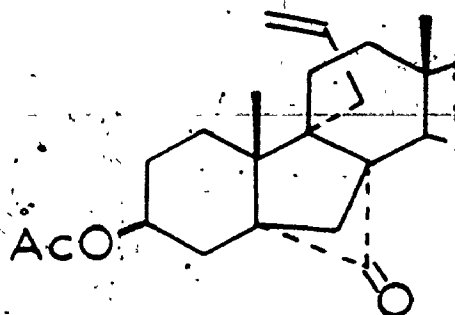
48a  $X = O; Y = H_2$

48b  $X = H_2; Y = O$



49a  $R = Ac$

49b  $R = H$



50

The  $\alpha$ -face product obtained in the case of 48a was interpreted as being a consequence of the ease of approach of allene from the less hindered side of this steroidal enone 48a. On the contrary, the  $\beta$  face of the  $\Delta^{8,9}$  double bond is blocked by angular methyl groups as a consequence of which no  $\beta$  face photoadduct is observed.

These steroidal enones 48a and 48b, seemed of interest in testing the efficiency of adsorption on silica gel in directing photocycloaddition. Specifically, we were concerned to know whether such adsorption, in the case of 48a, could lead to the formation of the hindered  $\beta$  adduct.

## RESULTS AND DISCUSSION

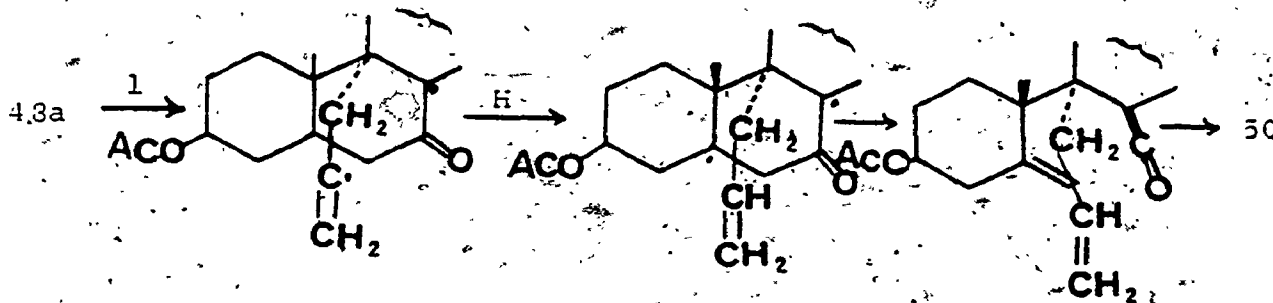
### 3.2 Photocycloaddition of $3\beta$ -acetoxy- $\Delta^{8,9}$ -cholesten-7-one (48a) and allene on silica

The photocycloaddition of  $3\beta$ -acetoxy- $\Delta^{8,9}$ -cholesten-7-one (48a) and allene adsorbed on silica gel was carried out using a 450 W medium pressure mercury lamp. The irradiation product was chromatographed to give the previously reported<sup>71</sup> rearrangement product (50) and an  $\alpha$ -adduct (49a)..

3.3 Structural determination of the reported photocycloadducts

a) Rearrangement photoadduct

In the I.R. spectrum of 50, a strong absorption was seen at  $1770\text{ cm}^{-1}$  and  $1735\text{ cm}^{-1}$  corresponding to the carbonyls of cyclobutanone and acetate functions, respectively. The  $^1\text{Hmr}$  spectrum showed a multiplet centred at  $\delta 5.0$  integrating to two hydrogens which was assigned to the olefinic hydrogens. The mass spectrum possessed the correct molecular ion at 482 a.m.u. The x-ray structure of this rearrangement product has been reported by Wiesner et al.<sup>71</sup>. Wiesner proposed the following mechanism for the formation of 50.



1 hv, allene

SCHEME XX

After an initial bonding of the  $\beta$  carbon of the steroidal enone 48a with the terminal position of allene, the alkenyl radical abstracts a hydrogen atom at C-5 and

further, the B ring of the steroid undergoes 1,4-cleavage followed by cyclization to give 50.

b) 8 $\alpha$ ,9 $\alpha$  Head-to-head allene photoadduct 49a

The I.R. spectrum of the known  $\alpha$ -adduct 49a exhibited strong absorption bands at 1730  $\text{cm}^{-1}$  and 1695  $\text{cm}^{-1}$  representing the acetate and carbonyl function respectively. In the  $^1\text{Hmr}$  spectrum of this compound two olefinic protons were represented by a broad signal at  $\delta$  4.6. The head-to-head regiochemistry was revealed by its medium intensity UV maximum at 290 nm ( $\epsilon$ 80), characteristic of a  $\beta\gamma$ -unsaturated ketone.

### 3.4 Structural determination of the new photoadducts

In addition to these known adducts, a mixture of three isomeric cycloadducts was also obtained in 70% yield. The complex mixture was not well resolved on tlc and was therefore converted to the corresponding alcohols by hydrolysis with methanolic KOH. This hydrolysed mixture was separated by preparative thin layer chromatography to give a crystalline adduct, identified below as a novel 1,3-allene photocycloadduct of 3 $\beta$ -acetoxy- $\Delta^{8,9}$ -cholesten-7-one, 48a, and a 1:1 mixture of two isomeric (2+2) allene-cyclic enone photoadducts.

a) 1,3 allene photocycloadduct 53a

The  $^{13}\text{Cmr}$  of the crystalline solid obtained above,

Figure 3.1 A view of 53c showing the molecular configuration. For clarity, the carbon and oxygen atoms are shown as spheres of arbitrary sizes; the oxygen atoms are hatched.

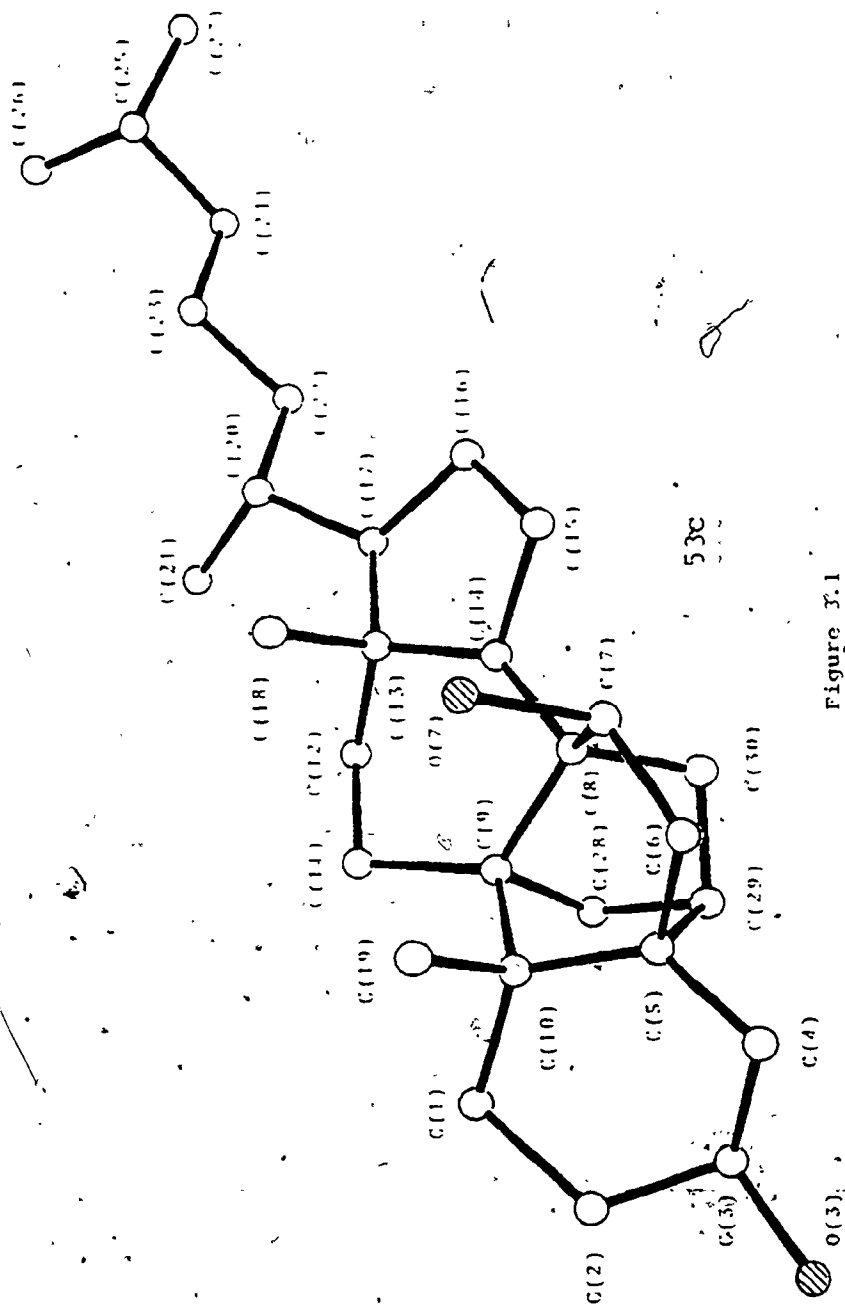


Figure 3.1

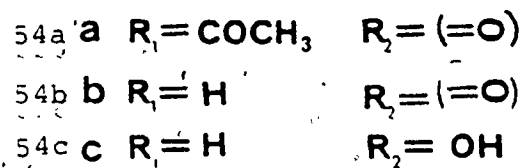
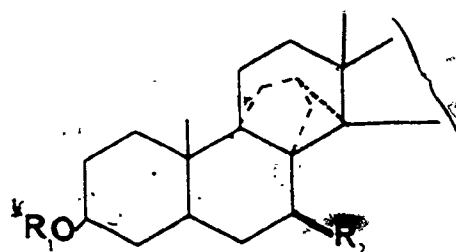
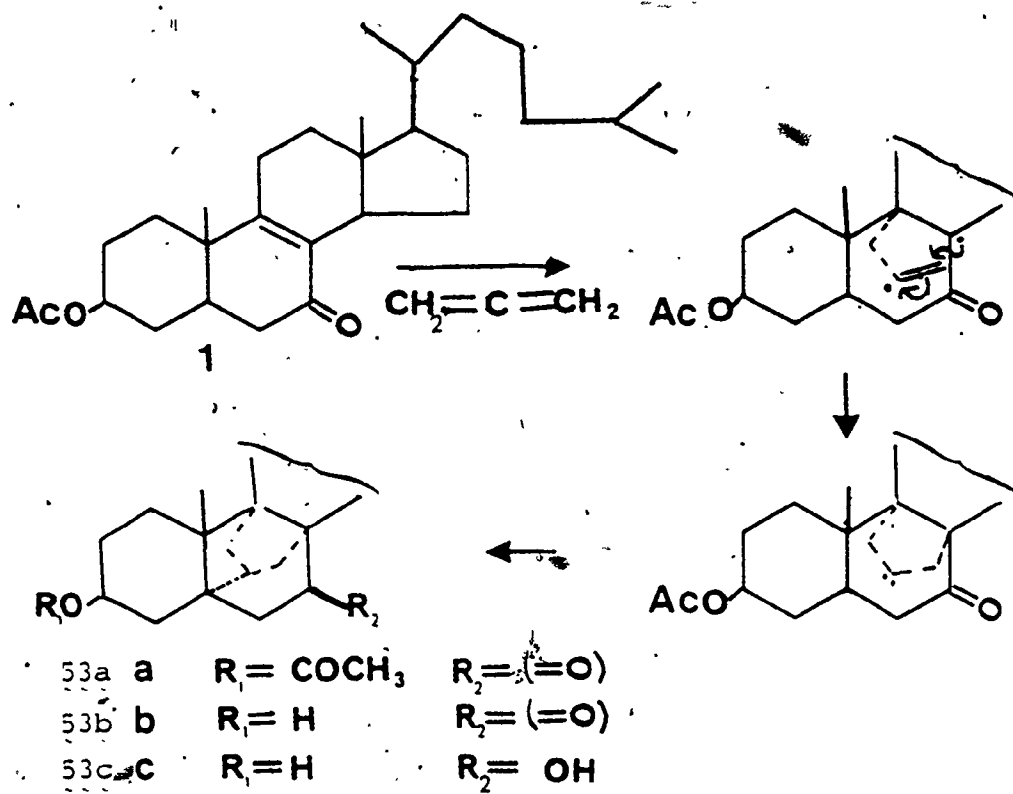
exhibited signals for five quaternary carbons, six methine and thirteen methylene carbons. No olefinic signals appeared in either the  $^{13}\text{Cmr}$  or  $^1\text{Hmr}$  spectra. Thus this unusual adduct (a hydroxyketone), now required to be hexacarbocyclic, was tentatively, on mechanistic grounds assigned structure 53b or 54b. The isolated yield of this derivative was 15% during silica gel irradiation of 48a to allene as compared to a yield of 6% from solution irradiation. Since a definitive structural assignment for this was not possible with the data available, an X-ray analysis was carried out. For obtention of suitable crystals the derived acetoxyketone was reduced with lithium-aluminium-hydride to give a pure diol as colourless granules. In the I.R. spectrum of this diol strong bands appeared at 3600, 3400  $\text{cm}^{-1}$  corresponding to the alcoholic function. The  $^1\text{Hmr}$  spectrum exhibited a doublet at  $\delta 4.1$  consistent with the new methine proton. The  $^{13}\text{Cmr}$  spectrum of this diol exhibited signals for five quaternary carbons, seven methines and thirteen methylene carbons. The carbonyl signal in  $^{13}\text{Cmr}$  was absent.

The X-ray analysis of the diol confirmed structure 53c, see fig. 3.1.<sup>+</sup> Since the diol has structure 53c,

---

<sup>+</sup> The X-ray analysis was done by Prof. G. Ferguson and Dr. Massod Parvez of the Department of Chemistry, University of Guelph, Guelph, Ontario, Canada N1G 2W1.





Scheme XIX

the hydroxyketone and acetoxyketone are 53b and 53a respectively. The crystal structure reveals the formation of three new C-C bonds to C(5), C(8), and C(9) on the  $\alpha$ -face of the steroidal framework proving attack by allene from the less hindered  $\alpha$ -face. The hydroxyl oxygen at C(7) is axial, and the bridged system is very strained.

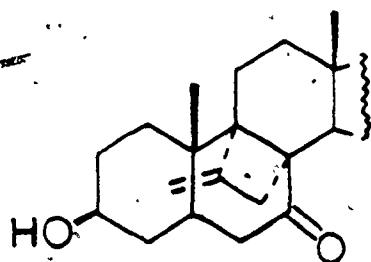
(b) Mechanism for the formation of a 1,3 allene-enone adducts (53a)

The mechanism for the formation of the 1,3 allene adduct 53a can be considered to proceed via overlap of an enone  $\alpha$  or  $\beta$  orbital with the terminal position of allene to give the normal triplet biradical intermediate. This may be then followed by overlap with the terminal orbital of the alkenyl radical to give directly the triplet carbene which can then undergo insertion, in partial analogy with oxacarbenes,<sup>84</sup> at the C<sub>5</sub> C-H bond to give the final product, as shown in Scheme XXI. This new adduct represents the first example of 1,3 photocycloaddition of allene to a cyclic enone 48a.

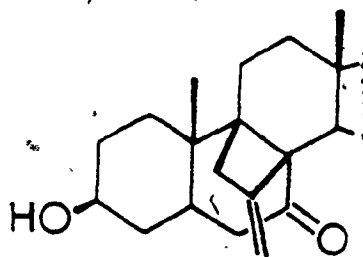
(c) (2+2) enone and allene photocycloadducts

The mixture of the alcoholic adducts was purified by flash chromatography giving a solid and a liquid adduct. That one photoproduct, 51, was an allene adduct followed from the mass spectrum ( $m/e$  440); <sup>1</sup>Hmr ( $\delta$  4.49, C=CH<sub>2</sub>) and <sup>13</sup>Cmr ( $\delta$  106.3, C=CH<sub>2</sub>). The head-to-head regiochemistry was revealed by its medium intensity UV maximum at 290 nm ( $\epsilon$ 96), characteristic of a  $\beta\gamma$  unsaturated ketone. The

photocycloadduct 52 was also an allene adduct, as judged from the mass spectrum ( $m/e$  440); the  $^1\text{Hmr}$  ( $\delta$ : 5.17, brs, 1H and 4.93 m, 1H,  $-\text{C}=\text{CH}_2$ ) and  $^{13}\text{Cmr}$  ( $\delta$ : 110.7,  $-\text{CH}_2$ ). This cycloadduct, 52, showed a very weak UV adsorption maximum at 290 nm ( $\epsilon$ 38), characteristic of an unperturbed carbonyl group, indicating it to be a  $\gamma\delta$  unsaturated ketone. The stereochemistry of addition in 51 and 52 became apparent from their  $^{13}\text{Cmr}$  spectra upon comparison with that for



52



51

derived alcohol 49b. In addition to the signals for the side chain carbons in each, there were several similarities in the spectra of 49b and 52 but very few for 49b and 51. For 49b and 52 the signals for five methylene, two methine and a quaternary centre differ by less than 0.1 ppm in the two spectra while the angular methyl, another methylene and quaternary signals fall between 0.2 ppm (see experimental). Thus, 12 of the 17 signals for the skeleton carbons were remarkably similar. In contrast, a single methylene absorption for compound 51 is found within 0.1 ppm of any of those for compounds 49b and 52; the

quaternary centers differ by 3-8 ppm, the methines by 3-10 ppm and the angular methyls by 1-2 ppm. On the basis of the  $^{13}\text{Cmr}$  data, combined with the above mentioned UV absorption it is concluded that 51 is the  $\beta$ -adduct with  $\beta\gamma$ -unsaturation and 52 is the regioisomeric  $\alpha$ -adduct with  $\gamma\delta$  unsaturation.

### 3.5 Mechanism for the formation of $\gamma\delta$ -unsaturated adduct

As pointed out in Chapter II an overlap of the  $\beta$  orbital of the  $\alpha,\beta$ -unsaturated ketone with the terminal allene carbon is required for the formation of a  $\beta\gamma$  allene cycloadduct (Wiesner's Proposal). Furthermore, it is known that ethyl, methyl and iso-propyl radicals add exclusively to the terminal carbon of allene,<sup>74</sup> owing to the fact that the  $\pi$  orbital of methylene groups in allene are orthogonal and the attack of a free radical on the central carbon resembles that of a primary radical rather than that of an allylic radical. The initially formed  $1^\circ$  radical undergoes a  $90^\circ$  rotation before benefiting from full allylic stabilization. The attack of the free radical on the central carbon is irreversible. By analogy with this radical like transition state, and assuming that attack at the terminal position of allene is unaffected by adsorption on silica gel, the formation of the  $\gamma\delta$  regioisomeric adduct 52 can be explained by assuming that initial bond formation occurs at the  $\alpha$  carbon of the steroidal enone 48a. (See Scheme 3.5)

### 3.6 Photocycloaddition of 3 $\beta$ -acetoxy- $\Delta^{8,9}$ -cholesten-11-one (48b) to allene

The photocycloaddition of 3 $\beta$ -acetoxy- $\Delta^{8,9}$ -cholesten-11-one (48b) to allene in methylene chloride was done using the reported procedure.<sup>71</sup> Thin layer chromatography of the crude product showed the presence of mainly unreacted starting unsaturated ketone 48b, with a minor compound (45%) less polar than 48b, as previously reported.<sup>71</sup> Irradiation of the same on silica gel did not lead to any noticeable change. The product obtained in minor amounts from silica gel and solution irradiation showed identical R<sub>f</sub> value on tlc. The photocycloaddition of 48b with allene on silica gel was slower than 48a, in agreement with Wiesner's observation in the case of homogeneous media.<sup>71</sup>

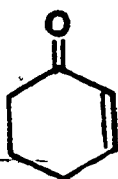
### Conclusion

The use of silica gel has thus induced photocycloaddition to the  $\beta$  face of the 8:9 double bond, and more importantly in reasonable amount:  $\beta$  photoadduct 51 represents about one third of the allene adducts formed. Aside from the exceptions reported for homogeneous systems it appears that the proposed stereochemical rule by Wiesner should also be applied to heterogeneous systems with caution.

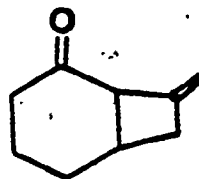
### 3.7 Formation of head-to-tail photoadducts on silica gel

In most of the cases reported in the literature the photocycloaddition of enones to allene results in the predominant formation of head-to-head (HH) regioisomers. There are few examples where the minor head-to-tail (HT) adduct has been characterized.<sup>47</sup> The reasons for the unusual preference for the formation of (HH) adducts are not yet understood.

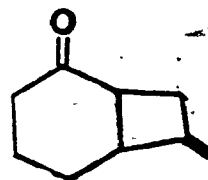
The formation of the head-to-tail adduct 52 on silica gel in the photocycloaddition of steroidal enone 48a to allene encouraged us to examine the photocycloaddition reactions of some simple cyclic enones to allene under heterogeneous conditions to determine the limits and utility of the reaction. The compounds chosen for photocycloaddition were cyclohexenone, 34 (disubstituted olefin), isophorone 56 (trisubstituted) and four bicyclic ketones 58, 60, 62, 64 (tetrasubstituted). Their photocycloaddition reactions with allene were carried out in solution ( $\text{CH}_2\text{Cl}_2$ ) and on dry silica gel. Except for the isophorone-allene cycloadduct mixture, which could be resolved on tlc, all the other adduct mixtures could not be resolved by glc or tlc for the determination of the ratio of the two regioisomeric adducts: the head-to-head, head-to-tail ratios in these mixtures were determined by integration of suitable signals in the  $^{13}\text{C}_{\text{Mg}}$  spectrum. The most reliable signal for the integration was the  $\text{sp}^2$  carbon



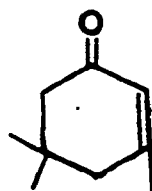
34



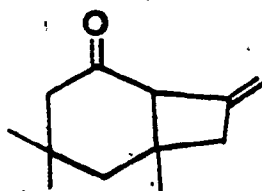
55a



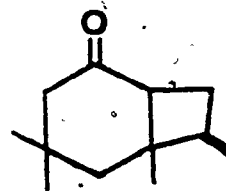
55b



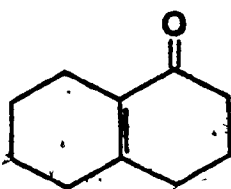
56



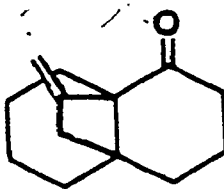
57a



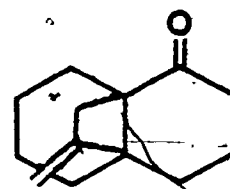
57b



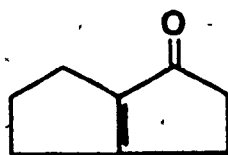
58



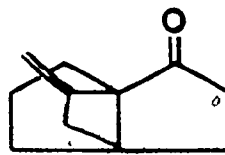
59a



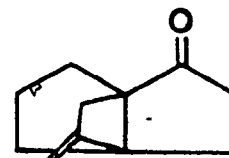
59b



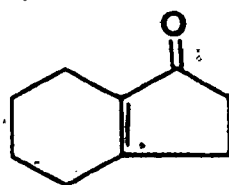
60



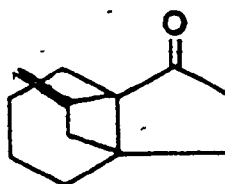
61a



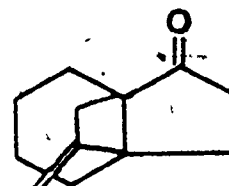
61b



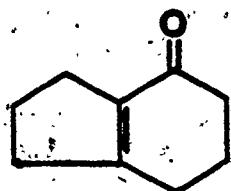
62



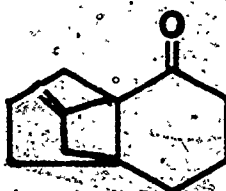
63a



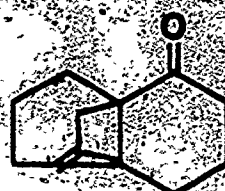
63b



64



65a



65b



2

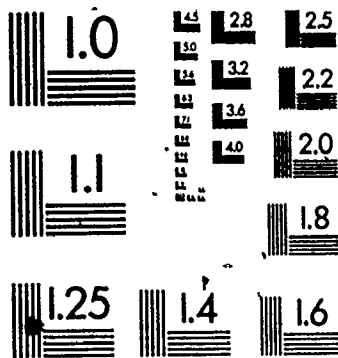


TABLE 3.1. CONDITIONS AND THE RESULTS OF THE CYCLOADDITION  
OF ENONES TO ALLENE.

Enone	System <sup>a</sup>	Product	Regioisomer (%) <sup>b</sup>	
			(HH)	(HT)
34	A	55a, 55b	94	6
	B	55a, 55b	65	35
56	A	57a, 57b	93	7
	B	57a, 57b	52, 59 <sup>c</sup>	48, 41 <sup>c</sup>
58	A	59a, 59b	70	30
	B	59a, 59b	34	66
60	A	61a, 61b	61	39
	B	61a, 61b	46	54
62	A	63a, 63b	75	25
	B	63a, 63b	32	68
64	A	65a, 65b	43	57
	B	65a, 65b	20	80

<sup>a</sup>A, methylene chloride solution, B, dry silica gel.

<sup>b</sup>Analysed by <sup>13</sup>Cmr (see text); estimated precision  $\pm 5\%$ .

<sup>c</sup>Relative ratio of isolated adducts after PTLC (preparative thin layer chromatography).

TABLE 3.2.  $^{13}\text{C}$  SHIELDING DATA<sup>a</sup> FOR PHOTOADDUCTS X-Y.

Cpd.	$\text{CH}_2=\text{C}-$	$\text{CH}_2=\text{C}-$	$\text{C}=\text{O}$
55a	108.1	144.7	208.9
55b	105.2	149.5	209.0
57a	108.2	142.3	209.8
57b	103.5	156.1	214.1
59a	105.8	147.7	212.6
59b	101.9	151.5	215.6
61a	109.8	145.4	216.5
61b	108.1	152.2	219.9
63a	106.6	145.2	219.6
63b	104.3	152.1	222.4
65a	108.1	146.3	215.1
65b	105.9	152.3	215.1

<sup>a</sup>In ppm from internal TMS in  $\text{CDCl}_3$ .

(=CH<sub>2</sub>) in each of the two adducts.

It is clear from the literature that the major product formed by photocycloaddition of allene to simple cyclopentenones and cyclohexenones in solution is the head-to-head adduct with cis-ring junction. Using this as a guide the carbon spectra of the six unsaturated ketone-allene photocycloaddition products were examined. For the total reaction products from solution irradiations the spectra showed the presence of two peaks, one of high and the other of low intensity, in the region  $\delta$  104-109 ppm. These were assigned to the =CH<sub>2</sub> signals of the major  $\beta\gamma$ -unsaturated ketone and the minor  $\gamma\delta$ -unsaturated ketone respectively (see Table 3.2 for chemical shifts). These two peaks were carefully integrated to obtain the ratio of  $\beta\gamma$  (head-to-head) and  $\gamma\delta$  (head-to-tail) adducts from the unsaturated ketones (34, 56, 58, 60, 62, and 64) from solution irradiation (Table 3.2). The same two peaks were also integrated for product mixtures derived from enone-allene irradiation on dry silica gel. The ratios obtained are listed in Table 3.1.

### 3.8 Photocycloaddition of allene to isophorone (56)

The photocycloaddition of allene to isophorone 56 in methylene chloride and on silica gel gave two cycloadducts (57a and 57b). The  $\beta\gamma$  adduct 57a showed a low field proton signal at  $\delta$  3.2, attributed to the methine proton at C-2:

an indication of head-to-head (HH) regiochemistry. In contrast, in the  $^1\text{Hmr}$  of 57b no low field signal was detected near 3.0 ppm, which indicated head-to-tail (HT) regiochemistry. Additional confirmation of these regiochemical assignments was obtained from the  $^{13}\text{Cmr}$  spectra of the two isomeric adducts. The assignment was made by comparisons with the data for similar analogues (Table 3.2).

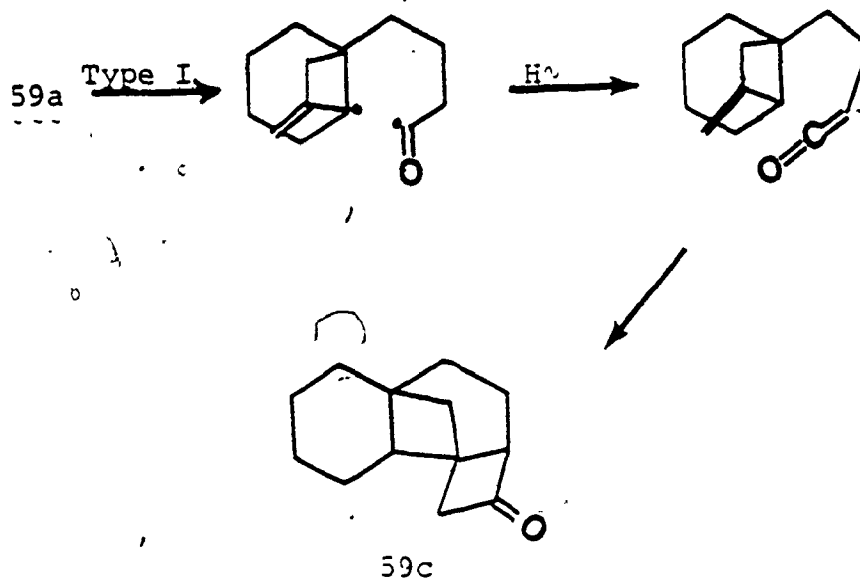
### 3.9 Photocycloaddition of allene to enones (34, 56, 58, 60, 62 and 64)

The photocycloaddition of enones (34, 56, 58, 60, 62 and 64) to allene in methylene chloride gave HH regioisomers as major photoadducts with the (HT) regioisomers also present in small amounts, as shown by  $^{13}\text{Cmr}$ . In contrast, irradiation of these enones and allene on silica produced a pronounced shift towards (HT) adduct formation. The formation of the head-to-tail (HT) product indicates a preference for reaction at the  $\alpha$  position of the enone with the terminal allene position, or reaction at the  $\beta$  position of the enone with the central position of the allene. Presumably the change is caused by changes in electron distribution induced by adsorption on to the silica gel surface, but no evidence is presently available to distinguish between these possibilities. In any event the ability to change the adduct composition may be of

synthetic utility.

### 3.10 Photocycloaddition of bicyclo[4.4.0]-dec-1(6)-en-2-one (58) to allene

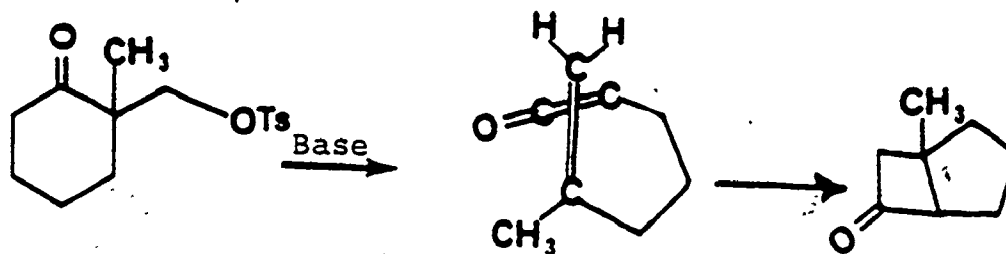
In the photocycloaddition of bicyclo[4.4.0]-dec-1(6)-en-2-one (58) to allene on silica gel there was obtained, in addition to the expected adducts 59a and 59b, -5% of a minor compound with the molecular formula  $C_{13}H_{18}O$ , i.e. isomeric with 59a and 59b. It appeared to contain a four-membered ring ketone since it exhibited carbonyl absorption at  $1760\text{ cm}^{-1}$  in the I.R. spectrum. The  $^{13}\text{Cmr}$  spectrum showed signals for a carbonyl carbon, two methine carbons, two quaternary carbons, and eight methylene carbons. The  $^1\text{Hmr}$  spectrum contained a one proton doublet at  $\delta\ 3.44\text{ ppm}$  ( $J=8\text{Hz}$ , 1H) and the AB part of an ABx system centred at  $\delta\ 2.78\text{ ppm}$  ( $J_{AB}=18\text{Hz}$ ,  $J_{AX}(\text{observed})=2.5\text{Hz}$ ,  $J_{BX}(\text{observed})=3\text{Hz}$ ). To determine the origin of this product, a mixture of photocycloadducts 59a and 59b was irradiated on silica gel and the irradiation mixture examined. It revealed, together with the major amounts of starting adducts 59a and 59b, about 5-10% of the cyclobutanone products. Thus, this compound is an over-irradiation product of 59a or 59b. Formation of this novel rearrangement product from 59a or 59b can be readily rationalized as follows.



Scheme XXII

a) Mechanism for the formation of 59c

Type I cleavage of 59a, followed by an intramolecular hydrogen transfer gives a ketene intermediate, which can subsequently undergo an allowed thermal ( $2\pi_s+2\pi_a$ ) cycloaddition to give the cycloadduct 59c. Close analogy with this thermal intramolecular cycloaddition has been reported in the literature<sup>85</sup> (see Scheme XXIII).



Scheme XXIII



## CHAPTER 4 - EXPERIMENTAL

### PART A

#### 4a.1 General

4a.1.1 Spectra: Ultraviolet spectra (UV) were recorded on a Varian Cary 219 Spectrophotometer. Routine <sup>1</sup>Hmr were recorded on a Varian T-60 instrument using tetramethylsilane as the internal standard. For more precise measurements a Varian XL-100 (100 MHz) was used. The I.R. spectra were recorded on a Beckman-Acculab 4 spectrophotometer. CD spectra were measured on a JASCO J5 spectrometer after calibration with d-camphorsulphonic acid.

4a.1.2 Melting Points: Melting points were measured on a Reichert hot stage or a Gallenkamp apparatus and are uncorrected.

4a.1.3 Gas Chromatography: G.C. analyses were performed on Varian-2400 instrument equipped with flame ionization detector and a 6'x2 mm glass column with 3% OV 101 on Chromosorb W.

4a.1.4 High Pressure Liquid Chromatography: HPLC analyses were performed on Waters HPLC equipment: LC system-441; 6000 A pump; 730 data module with  $\mu$ -Porasil silica column.

#### 4a.2 Materials

4a.2.1 Solvents: All solvents used for solution irradiation or for preparation of silica gel samples were Fisher spectrograde. Methylene chloride was dried over  $\text{CaH}_2$ .

4a.2.2 Adsorbents: Merck silica gel 60 (E.M. Merck, 35-70 mesh) and alumina (neutral, ICN Pharmaceutical) were used in all irradiation experiments. Thin layer chromatography (tlc) was on Kiesel gel 60 PF<sub>254</sub> plates and flash chromatography (FC) columns were prepared as described.<sup>86</sup>

4a.2.3 Gases: Allene (Matheson) and ethylene (Canadian Liquid Air) were used directly from the cylinder.

#### 4a.2.4 Commercially available Enones: Testosterone

propionate: Testosterone propionate (BDH) was recrystallized from ethyl acetate: mp 117-119°C.

Testosterone: Testosterone was recrystallized from methanol: mp 151-152°C. 3 $\beta$ -acetoxypregna-5,16-

dien-20-one: 3 $\beta$ -acetoxypregna-5,16-dien-20-one (Steraloids) was recrystallized before use mp 172-174°C.

#### 4a.2.5 Enones Synthesized:

Preparation of  $\Delta^{4,6}$ -androstadien-3-one-17 $\beta$ -ol-propionate (26).

The procedure of Agnello and Laubach<sup>75</sup> was followed. A

stirred mixture of 500 mg (1.76 mmol) of testosterone propionate, 15a and 1.2 g (4.9 mmol) of chloranil in 20 mL of *t*-butanol was heated at reflux temperature for 3h. The excess chloranil was filtered and the filtrate taken to dryness. The residue was taken up in chloroform (30 mL) and the solution washed with 30 mL portions of water (3 times), 5% sodium hydroxide solution and again with water. Evaporation of the chloroform afforded a crystalline residue, when triturated, yielded 722 mg of crude residue. Purification by PTLC (7/3 (v/v) hexane-ether) gave 434 mg (71.9%) of 26 mp 131-133°C (lit.<sup>75</sup> 135-136°C); <sup>1</sup>Hmr(CDCl<sub>3</sub>) δ 6.05 (s, 2H), 5.75 (s, 1H), 1.0 (s, 3H), 0.90 (s, 3H); IR (CHCl<sub>3</sub>) ν<sub>max</sub> 1735, 1670 cm<sup>-1</sup>; exact mass calcd. for C<sub>22</sub>H<sub>30</sub>O<sub>3</sub> 342.2195, obsd. 342.2193.

#### Preparation of 17β-Acetoxy-5α-androst-1-en-3-one (30b)

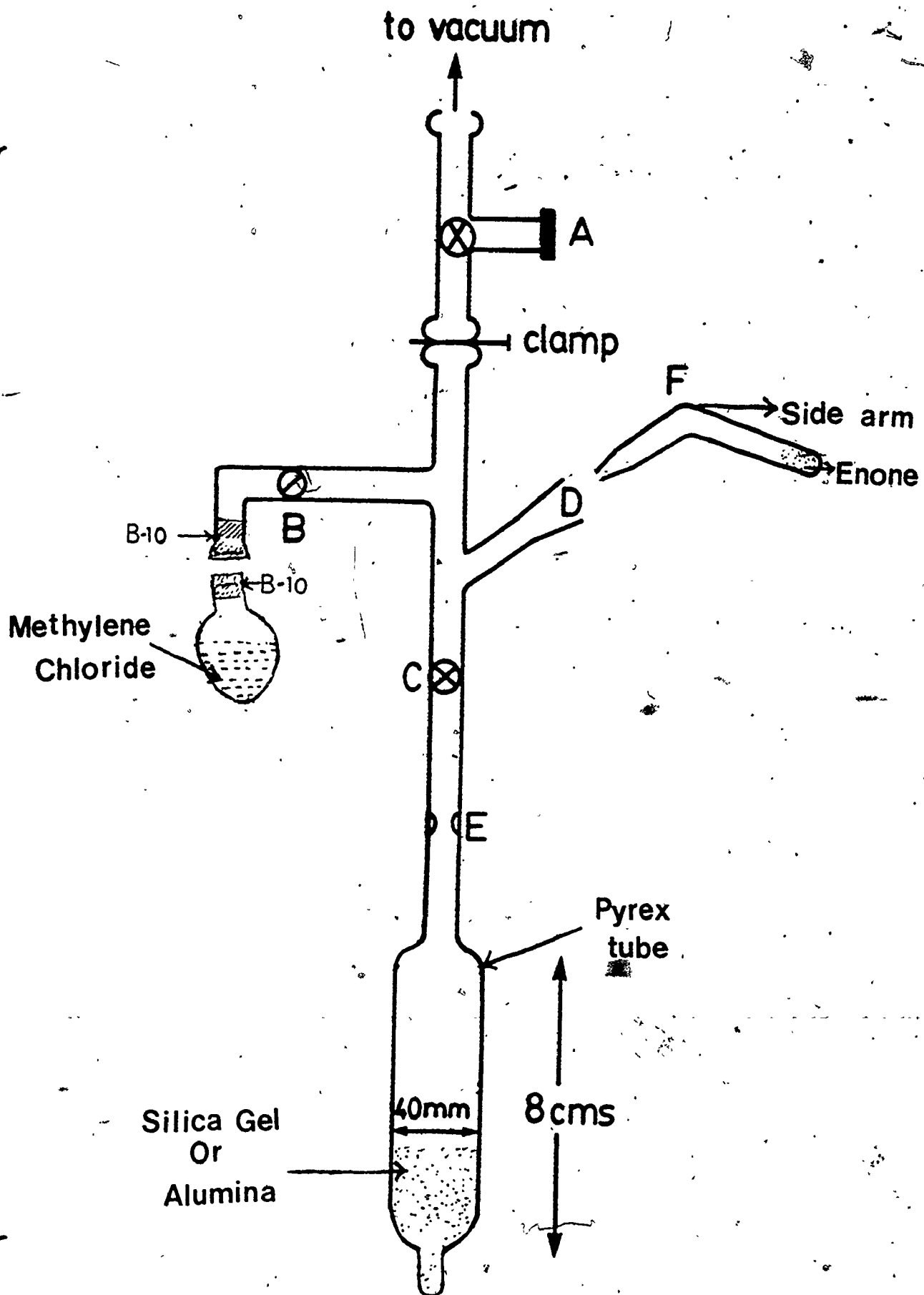
The following literature procedure for the preparation of 30b was used.<sup>77</sup> A stirred mixture of 356 mg (1.1 mmol) androstanolone (29) and DDQ (1.4 mmol) in 10 mL dioxane was heated at reflux for 10 h. The solution was taken to dryness and acetylated with Ac<sub>2</sub>O and pyridine. Purification of the resulting residue by PTLC gave 75 mg (21%) of 30b. mp. 124-126°C (lit.<sup>77</sup> 125-128°C); IR(CHCl<sub>3</sub>) 1720, 1665 cm<sup>-1</sup>; <sup>1</sup>Hmr (CDCl<sub>3</sub>) δ 7.2 (d, 1H, J≈10Hz), 5.9 (d, 1H, J≈10Hz), 1.0 (s, 3H), 0.9 (s, 3H); exact mass calcd. for C<sub>21</sub>H<sub>30</sub>O<sub>3</sub> 330.2195, obsd. 330.2194.

#### 4a.3 Procedure for Silica gel and Alumina Experiments

##### 4a.3.1 Procedure for sample preparation and irradiation on dry silica gel

A preweighed sample of silica gel (-3g) was introduced into a Pyrex tube equipped with a side arm in apparatus illustrated in Fig 4.1 and to it was added a sample of enone (0.1 mmol). With stopcocks A and C open to the pump and B and D closed the gel was heated at 200°C (1 mm Hg, 3h). The silica gel was allowed to cool to room temperature under vacuum, C was then opened and the enone was dropped onto the gel and dry methylene chloride (25 mL) was condensed onto the gel by cooling the Pyrex cylinder containing the silica gel at -78°C. The slurry was shaken well in order to dissolve the enone and the receiver attached to B was then cooled and the solvent was distilled back to the original container. Finally, with B closed and A opened to the pump, the gel was degassed at 1 mm Hg for -6h. In the case of cyclopentene a preweighed sample (-1 mmol) was condensed into the Pyrex cylinder cooled to -78°C. In the case of gases (ethylene and allene), the Pyrex cylinder, containing gel and enone, of total capacity -43 mL was cooled to 0°C and the gas was introduced at 1 atm pressure. The Pyrex cylinder was then sealed and rotated on its long axis in front of 450 W medium pressure Hg lamp. The low temperature irradiation was performed by rotating the Pyrex cylinder immersed in methanol/dry ice bath. Irradiation times varied considerably depending upon

Figure 4.1: Apparatus for preparation of dry Silica gel  
and Alumina samples.



the substrate and conversion required.

#### 4a.3.2 Quantitative product analysis

After extracting the silica gel with ether and with methanol the irradiation products were analysed by G.C. or HPLC. In G.C. analyses, a known amount of internal standard (Androsta-1,4-diene-3-one-17 $\beta$ -ol) was added to the concentrated irradiation mixture. The sample was analysed, taking an average of at least two injections for each determination. A calibration response curve was constructed for each compound analysed. The response factor for an enone was obtained as the slope of a plot of mol of enone/mol of standard versus peak area of enone/peak area of standard. The response factor was used to calculate the amount of enone in a reaction mixture.

#### 4a.3.3 Procedure for sample preparation and irradiation on alumina

A preweighed sample of alumina (-3g) was dried overnight in an oven at 200°C. The alumina sample was then allowed to cool to room temperature and transferred to a Pyrex cylinder: the remainder of the procedure were as outlined for silica gel.

#### 4a.3.4 Irradiations on silica gel

Eight to nine grams of silica, enone(1-2 mmol) and methylene chloride (30mL) were introduced into a Pyrex

cylinder of total capacity 88 mL. After evaporating the solvent, olefin was introduced as described previously. For all the compounds isolated appropriate spectra and precise masses were recorded.

#### 4a.3.4 Solution irradiations

A solution of enone (-0.05M) in ethyl acetate or methanol was irradiated while a continuous stream of ethylene or allene was bubbled through the solution. In the case of cyclopentene, a preweighed amount was added to the enone solution in the required solvent. The low temperature irradiation was performed by immersing the Pyrex tube in a dry ice-methanol bath.

#### 4a.5 PREPARATION OF STEROIDAL ENONES PHOTOADDUCTS

##### Photocycloaddition of testosterone propionate (15a) to ethylene

A solution of 680 mg (1.97 mmol) of testosterone propionate, 15a in 10 mL of ethyl acetate was irradiated while a continuous stream of ethylene was bubbled through the solution for 3h. Flash chromatography of the irradiation products on silica using 7:3 (v/v) petroleum ether-ether gave 160 mg of 16a as a white crystalline solid: mp 184-185°C (lit.<sup>63</sup> 187-188°C); [<sup>1</sup>Hmr (CDCl<sub>3</sub>) δ 4.60 (t, 1H), 0.83 (s, 6H); IR(CHCl<sub>3</sub>) ν<sub>max</sub> 1725, 1690 cm<sup>-1</sup>; mass spectrum (70 eV) (rel. intensity) 372 (21%) 354 (34%), 344 (42%), 57 (100%)] together with 195 mg of mixed isomers



and 250 mg of 16c [mp 148-151°C (lit.<sup>63</sup> 152-153°C);  $^1\text{Hmr}$  ( $\text{CDCl}_3$ )  $\delta$  4.83 (t, 1H), 1.00 (s, 3H), 0.80 (s, 3H); IR ( $\text{CHCl}_3$ )  $\nu_{\text{max}}$  1720  $\text{cm}^{-1}$ ; mass spectrum (70 eV) m/e (rel. intensity) 372 (34%), 344 (50%), 57 (100%)] . Flash chromatography of the mixed fractions gave 10 mg of 16b containing ~10% of 16a as an impurity, as shown by HPLC: mp. 72-75.5°C (lit.<sup>63</sup> 73-75°C);  $^1\text{Hmr}$  ( $\text{CDCl}_3$ )  $\delta$  4.6 (t, 1H), 0.83 (s, 6H); IR ( $\text{CHCl}_3$ )  $\nu_{\text{max}}$  1725, 1680  $\text{cm}^{-1}$ ; mass spectrum (70 eV) m/e (rel. intensity) 372 (20%), 57 (100%);  $\text{CD}(\text{CH}_3\text{OH})[\theta]_{290} - 1766$ . Isomerization of 16c to 16b was accomplished by the literature procedure.<sup>63</sup> G.C. analyses (column temp. 230°C) of the irradiation products were complicated by the thermal isomerization of 16c to 16b. The isomeric adducts were separable by analytical HPLC using benzene-ethyl acetate 9.5/0.5 (v/v). The retention times for the individual peaks were correlated with the authentic samples.

The photocycloaddition of 15a and ethylene on silica gel was performed as previously described and the products analysed (HPLC).

#### Photocycloaddition of testosterone propionate (15a) to cyclopentene

Irradiation of testosterone propionate, 15a (350 mg, 1.0 mmol) and 4 mL (45 mmol) of cyclopentene was performed by the literature procedure.<sup>63</sup> The residue after the distillation of cyclopentene, was crystallized from ethyl

acetate to give 45 mg of 17a: mp 217-218°C (lit.<sup>63</sup> 215-217°C); <sup>1</sup>Hmr (CDCl<sub>3</sub>) δ 4.60 (m, 1H), 0.86 (s, 3H), 0.82 (s, 3H); IR(CHCl<sub>3</sub>) ν<sub>max</sub> 1680, 1720 cm<sup>-1</sup>; CD(CH<sub>3</sub>OH) [θ]<sub>292</sub> +7093; mass spectrum (20 eV) m/e (rel. intensity) 345 (100%), 340 (73.5%), 325 (94%). Chromatography of the mother liquor by flash column using 7:3 (v/v) petroleum ether-ether gave an additional 40 mg of 17a, 35 mg of 17b previously unreported,<sup>63</sup> mp 151-155°C; <sup>1</sup>Hmr(CDCl<sub>3</sub>) δ 4.50 (m, 1H), 0.90 (s, 3H), 0.83 (s, 3H); IR(CHCl<sub>3</sub>) ν<sub>max</sub> 1680, 1720 cm<sup>-1</sup>; CD(CH<sub>3</sub>OH) [θ]<sub>294-6511</sub>; mass spectrum (20 eV) m/e (rel. intensity) 412 (41%), 345 (100%); exact mass calcd. for C<sub>27</sub>H<sub>40</sub>O<sub>3</sub> 412.2977, obsd. 412.2970, retention time on G.C. at 240°C: 32 minutes and 110 mg of 17c: mp. 166.5 - 167.5° (lit.<sup>63</sup> 168-169.5°C); <sup>1</sup>Hmr(CDCl<sub>3</sub>) δ 4.46 (m, 1H), 2.96 (s, 2H), 1.10 (s, 3H), 0.80 (s, 3H); IR(CHCl<sub>3</sub>) ν 1710 cm<sup>-1</sup>; CD(CH<sub>3</sub>OH) [θ]<sub>288</sub> + 27,486; mass spectrum (20 eV) m/e (rel. intensity) 412 (80.6%), 345 (100%), 340 (55.6%), 325 (97.5%).

#### Irradiation of testosterone propionate (15a) and cyclopentene on silica gel

Irradiation of 700 mg (2 mmol) of 15a and 358 mg (5 mmol) of cyclopentene on 10.5 g of silica gel gave 714 mg of an oil. Flash chromatography, as outlined above, gave 51 mg of 17a, 109 mg of mixed isomers and 48 mg of 17b.

### Thermal isomerization of 17c to 17d

Isomerization of 17c to 17d was accomplished by the literature procedure.<sup>63</sup> A sample of 17c (13 mg, 0.3 mmol) of was heated in a sealed tube at 250°C for 1 h. Crystallization from methanol gave an analytically pure sample of 17d: mp 139-140°C (lit.<sup>63</sup> 140-141°C); IR(CHCl<sub>3</sub>)  $\nu_{\max}$  1680, 1720 cm<sup>-1</sup>; <sup>1</sup>Hmr (CDCl<sub>3</sub>)  $\delta$  4.5 (m, 1H), 0.90 (s, 3H), 0.83 (s, 3H); CD(CH<sub>3</sub>OH) [ $\theta$ ]<sub>294</sub> -7772; mass spectrum (20 eV) m/e (rel. intensity) 412 (41%), 345 (100%), tlc 7:3 (v/v) petroleum ether-ether Rf 0.38; Retention time on G.C. at 240°C:23 minutes. The cycloadduct 17b isolated from photocycloaddition in solution and on silica showed different Rf value on tlc, retention time on G.C. and the mp than 17d isolated from the thermal isomerization of trans adduct 17c.

### Irradiation of testosterone propionate (15a) and allene on silica gel

Irradiation of 15a (157 mg, 0.45 mmol) and allene on 7.8 g of silica gave 190 mg of oil. Flash chromatography on silica using 8:2 (v/v) petroleum ether-ether gave 61 mg of 18a as a white crystalline solid: [mp 148.5-150°C; <sup>1</sup>Hmr (CDCl<sub>3</sub>)  $\delta$  4.96 (brs, 2H), 4.43 (t, J = 8Hz, 1H), 3.06 (m, 1H), 0.90 (s, 3H), 0.83 (s, 3H); IR(CHCl<sub>3</sub>)  $\nu_{\max}$  1725, 1690, 900 cm<sup>-1</sup>; UV(CH<sub>3</sub>OH) 293 nm ( $\epsilon$ 187); CD(CH<sub>3</sub>OH) [ $\theta$ ]<sub>292</sub> + 2128; exact mass calcd. for C<sub>25</sub>H<sub>36</sub>O<sub>3</sub> 384.2664; obsd. 384.2660] together with 19 mg of mixed isomers, 58 mg of 18b [mp

103.5°-105°C;  $^1\text{Hmr}$  ( $\text{CDCl}_3$ ) 4.90 (brs, 2H), 4.53 (t,  $J = 8\text{Hz}$ , 1H), 3.13 (m, 1H), 0.93 (s, 3H), 0.83 (s, 3H); IR ( $\text{CHCl}_3$ )  $\nu_{\text{max}}$  1730, 1690, 900  $\text{cm}^{-1}$ ; UV( $\text{CH}_3\text{OH}$ ) 295 nm ( $\epsilon 180$ ); CD( $\text{CH}_3\text{OH}$ ) $[\theta]_{292-2523}$ ; exact mass calcd. for  $\text{C}_{25}\text{H}_{36}\text{O}_3$  384.2664; obsd. 384.2657 and 12 mg of 18c: mp 79-81°C;  $^1\text{Hmr}$  ( $\text{CDCl}_3$ )  $\delta$  4.93 (brs, 2H), 4.47 (t,  $J = 8\text{Hz}$ , 1H), 1.0 (s, 3H), 0.76 (s, 3H); IR( $\text{CHCl}_3$ )  $\nu_{\text{max}}$  1720, 1680, 900  $\text{cm}^{-1}$  UV( $\text{CH}_3\text{OH}$ ) 284 nm ( $\epsilon 30.7$ ); CD( $\text{CH}_3\text{OH}$ ) $[\theta]_{284-1256}$ ; exact mass calcd. for  $\text{C}_{25}\text{H}_{36}\text{O}_3$  384.2664; obsd. 384.2659. G.C. analyses of the crude irradiation product showed two peaks with ratio -1:1.

The photocycloaddition of 15a and allene in methanol or ethyl acetate was performed as previously described and the products analysed (G.C.).

#### Photocycloaddition of testosterone (15b) to allene

The photocycloaddition of 15b and allene in methanol, on silica and alumina was performed as previously described. The irradiation products were treated with propionic anhydride and pyridine (overnight at room temperature) and the products analysed (G.C.).

The photocycloaddition of 20 mg (0.056 mmol) of 15b and allene in 2 mL acidic methanolic solution ( $\text{HCl}$ , pH = 3) was performed and no difference in behaviour than in methanol was observed.

**Photocycloaddition of 17-epitestosterone (15c) to allene**

Irradiation of 6 mg (0.02 mmol) of 15c and allene in methanol, on silica and alumina was performed as outlined above. The resulting yellow residue was oxidized with 10% sodium dichromate solution in  $\text{CH}_2\text{Cl}_2$ , to the corresponding dione cycloadducts 19a - 19c. Exact mass calcd. for  $\text{C}_{22}\text{H}_{30}\text{O}_2$  326.2246, obsd. 326.2246.

Irradiation products from the photocycloaddition of 15b and allene were similarly oxidized to the cycloadducts 19a - 19c as shown by retention times on G.C. and Rf. values on tlc: exact mass calcd for  $\text{C}_{22}\text{H}_{30}\text{O}_2$  326.2246 obsd. 326.2246.

**Photocycloaddition of 12-methoxy-18,19-bisnorpodocarpa-4,8,11,13-tetraen-3-one (24)<sup>†</sup> to allene**

Irradiation of 150 mg (0.6 mmol) of 24 and allene at  $-78^\circ\text{C}$  in methylene chloride gave a yellow oil which was crystallized from methanol to give 40 mg of 25a: mp  $70-72^\circ\text{C}$ ;  $^1\text{Hmr}$  ( $\text{CDCl}_3$ )  $\delta$  7.12-6.64 (m, 3H), 5.06-4.88 (m, 2H), 3.78 (s, 3H), 1.12 (s, 3H); IR( $\text{CHCl}_3$ )  $\nu$  1685, 900  $\text{cm}^{-1}$ ; exact mass calcd. for  $\text{C}_{19}\text{H}_{22}\text{O}_2$  282.1620, obsd. 282.1616. Chromatography of the mother liquid by PTLC (9:1 (v/v) ether-hexane, 11 developments) gave an additional 38

---

<sup>†</sup> The author is thankful to Prof. R.B. Kelly, Department of Chemistry, University of New Brunswick, Canada for the generous supply of the enone.

mg of 25a and 12 mg of 25b as an oil:  $^1\text{Hmr}$  ( $\text{CDCl}_3$ ) 7.12-6.64 (m, 3H), 5.06-4.88 (m, 2H), 3.78 (s, 3H), 1.12 (3H); IR( $\text{CHCl}_3$ ) 1690, 900  $\text{cm}^{-1}$ ; exact mass, calcd. for  $\text{C}_{19}\text{H}_{22}\text{O}_2$  282.1620, obsd. 282.1620; 2,4-dinitrophenyl--hydrazone mp 102-104°C; exact mass, calcd. for  $\text{C}_{25}\text{H}_{26}\text{N}_4\text{O}_5$  462.1903, obsd. 462.1903, temperature for G.C. analysis: 195°C.

The photocycloaddition of 24 and allene on silica gel was performed as described previously and the products analysed by G.C.

Irradiation of  $\Delta^{4,6}$ -androsta-3-one-17 $\beta$ -ol-propionate (26) and cyclopentene on silica gel.

Irradiation of 26 (260 mg, 0.76 mmol) and cyclopentene (250 mg, 3.6 mmol) on 10 g of silica gave 312 mg of yellow oil. Purification by PTLC (6/4 (v/v) hexane-ether, 3 developments) gave 29 mg of 27b [mp 160-163°C;  $^1\text{Hmr}$  ( $\text{CDCl}_3$ )  $\delta$  5.7 (brs, 1H), 4.7 (m, 1H); IR( $\text{CHCl}_3$ ) 1655, 1720  $\text{cm}^{-1}$ ; UV( $\text{CH}_3\text{OH}$ ) 255 nm ( $\epsilon$  12000); exact mass calcd. for  $\text{C}_{27}\text{H}_{38}\text{O}_3$  410.2820, obsd. 410.2820]. 61 mg of 27a [mp 161 - 163°C (lit.<sup>63</sup> 164.5 - 165.5°C);  $^1\text{Hmr}$  ( $\text{CDCl}_3$ ) 5.9 - 5.7 (ABx,  $J_{AB} = -10$  Hz,  $J_{AX} = -2.5$  Hz,  $J_{BX} = -3$  Hz, 2H), 4.6 (m, 1H); exact mass calcd. for  $\text{C}_{27}\text{H}_{38}\text{O}_3$  410.2820, obsd. 410.2820] 118 mg of 26, and 6 mg of unidentified cycloadduct as an oil: exact mass calcd. for  $\text{C}_{27}\text{H}_{38}\text{O}_3$  410.2820, obsd. 410.2820.

**Photocycloaddition of  $\Delta^{4,6}$ -androsta-3-one-17 $\beta$ -ol-propionate (26) to cyclopentene**

Irradiation of 26 (85 mg, 0.76 mmol) and cyclopentene (1 mL) in 1 mL benzene was carried out by the literature procedure.<sup>63</sup> Purification by PTLC (6/4 (v/v) hexane-ether, 2 developments) gave 63 mg of 27a. mp, IR, NMR and precise mass were as outlined above.

**Epimerization of trans-adduct 27a to cis-adduct 27c**

Epimerization of trans-photoadduct 27a to cis-photoadduct was accomplished by the literature procedure.<sup>63</sup> A solution of 8 mg (0.02 mmol) of cyclopentene adduct 27a in 2 mL of methanol containing 10% aqueous potassium hydroxide solution was allowed to stand overnight at room temperature. After neutralizing the solution with dil HCl, the methanol was removed and the residue dissolved in chloroform. The organic layer was washed twice with water, saturated sodium chloride solution and dried. The resulting solid was propionylated by treating it with propionic anhydride and pyridine to give a white solid after usual work-up. Crystallization from methanol gave the analytical sample of 27c, mp 106-108°C (lit<sup>63</sup> 108-109°C); exact mass calcd. for C<sub>27</sub>H<sub>38</sub>O<sub>3</sub> 410.2820; found 410.2820.

**Photocycloaddition of 17 $\beta$ -Acetoxy-5 $\alpha$ -androst-1-en-3-one (30b) to cyclopentene**

Irradiation of 30b (50 mg, 0.15 mmol) in cyclopentene-ethyl acetate (6:4 (v/v)) was performed by the literature procedure.<sup>78</sup> TLC showed the presence of a major and a minor photoadduct. G.C. analyses also showed the presence of a major photocycloadduct as reported.<sup>78</sup>

Irradiation of 30b (20 mg, 0.06 mmol) on 1 g of silica was performed as previously described. After 30 h of irradiation the G.C. analysis showed 10% conversion. The reaction was not pursued further. Mass spectrum showed the addition of cyclopentene, exact mass calcd. for C<sub>26</sub>H<sub>38</sub>O<sub>3</sub> 398.2821, obsd. 398.2820.

**Photocycloaddition of 3 $\beta$ -acetoxypregna-5,16-dien-20-one (31a) to ethylene**

Irradiation of 31a (100 mg, 0.28 mmol) and ethylene on 8 g of silica gave an oil. The resulting oil was purified by PTLC (9/1 (v/v) benzene-ethyl acetate, 3 developments) to give 21 mg of 32a as a white crystalline solid: mp 187-190°C (lit<sup>65</sup> 186-187°C); [<sup>1</sup>Hmr  $\delta$  2.0 (s, 6H), 1.05 (s, 3H), 0.6 (s, 3H); IR(CHCl<sub>3</sub>)  $\nu$  1730, 1690 cm<sup>-1</sup>] 14 mg of 32b: [mp 193-194°C (lit<sup>65</sup> 195-196°C); <sup>1</sup>Hmr (CDCl<sub>3</sub>)  $\delta$  2.02 (s, 6H), 1.16 (s, 3H), 1.04 (s, 3H); IR(CHCl<sub>3</sub>)  $\nu$  1730, 1690 cm<sup>-1</sup>; mass spectrum m/e 324 (100%) and 35 mg of 31a was recovered.

The photocycloaddition of 31a and ethylene in methanol



or benzene was performed as previously described and the products analysed by G.C.

**Photocycloaddition of 3 $\beta$ -hydroxypregna-5,16-dien-20-one (3lb) to ethylene**

The photocycloaddition of 3lb and ethylene in methanol and on silica was performed as outlined above. The irradiation mixture was treated with acetic anhydride and pyridine and products analysed by G.C. (column temp. 210°C).

## PART B

## 4b.1 General

## 4b.1.1 N.M.R. Spectrum

$^1\text{H}$ mr spectra were recorded on a Varian XL-100 (100 MHz) or an XL-200 (200 MHz). The latter instrument was used to record the  $^{13}\text{C}$  spectra (50.3 MHz) and comparison of the fully decoupled spectra with those obtained with either the APT-(87) or INEPT (88) sequence served to identify the methyl, methylene, methine and quaternary signals. Chemical shifts are reported in parts per million (ppm) on the  $\delta$  scale relative to  $(\text{CH}_3)_4\text{Si}$  as internal standard.

## 4b.1.2 Compounds Used

Cyclohexenone: Cyclohexenone was distilled before use.

isophorone: isophorone was distilled before use.

The following compounds were kindly prepared by Dr. Vinod Dave by the known methods and gave satisfactory physical and spectral data:  $3\beta$ -acetoxy- $\Delta^{8,9}$ -cholesten-7-one, 48a,<sup>89</sup>  $3\beta$ -acetoxy- $\Delta^{8,9}$ -cholesten-11-one, 48b,<sup>90</sup> bicyclo[4.4.0] dec-1(6)-en-one, 58,<sup>91</sup> bicyclo[3.3.0]- $\Delta^7$ -octen-1(5)-en-2-one, 60,<sup>91</sup> 4,5,6,7-tetrahydroindan-1-one, 62,<sup>91</sup> and  $\Delta^8$ -hydrindenone 64.<sup>91</sup>

## 4b.1.3 Procedure for sample preparation and irradiation on dry silica

The procedure for sample preparation in the case of

steroidal enones 48a and 48b was as outlined in section 4a.3.1. In the case of liquid enones (34, 56, 58, 60, 62, and 64) a preweighed sample (0.1 mmol) was condensed into the Pyrex cylinder containing silica gel cooled to  $-78^{\circ}\text{C}$ . The irradiation procedure was as outlined in section 4a.3.1.

#### 4b.1.4 Solution irradiation

A solution of enone (0.05 M) in methylene chloride was irradiated while a continuous stream of allene was bubbled through the solution.

#### 4b.1.5 Sample analysis

The silica gel was extracted with ether and with methanol. The adduct products, except in the case of 48a and 48b, were analyzed by  $^{13}\text{Cmr}$  using  $\text{sp}^2$  carbon atoms ( $=\text{CH}_2$ ) as probes.

#### 4b.2 ADDUCT PRODUCTS

##### 4b.2.1 Photocycloaddition of 3 $\beta$ -acetoxy- $\Delta^{8,9}$ -cholesten-7-one (48a) to allene on silica gel

Irradiation of 48a (200 mg, 0.45 mmol) and allene on 6 g of silica gave 190 mg of yellow oil which was purified by PTLC (6/4 (v/v) hexane-ether, 7 developments). The band at  $R_f$  0.81 gave 12.3 mg of colourless solid. One recrystallization from ether-methanol gave 7.6 mg of 50: mp  $175.5\text{--}177^{\circ}\text{C}$  (lit<sup>71</sup>  $177\text{--}178^{\circ}\text{C}$ ); IR ( $\text{CHCl}_3$ )  $\nu_{\text{max}}$  1770,  $1730\text{ cm}^{-1}$ ;  $^1\text{Hmr}$  ( $\text{CDCl}_3$ )  $\delta$  5.58 (brs, 1H), 5.12 – 4.48 (m,

2H), 2.06 (s, 3H); exact mass calcd. for  $C_{32}H_{50}O_3$  482.3759, found 482.3743. The band at Rf 0.74 gave 23 mg of the reported  $\alpha$  adduct 49a: mp 116-118°C (lit<sup>71</sup> 119.5 - 120.5°C);  $^1H$ mr ( $CDCl_3$ )  $\delta$  4.6 (brs, 2H), 2.0 (s, 3H); UV ( $CH_3OH$ ) 290 nm ( $\epsilon$ 86); exact mass calcd. for  $C_{32}H_{50}O_3$  482.3759, found 482.3749; derived hydroxyketone 49b:  $^{13}C$ mr ( $CDCl_3$ )  $\delta_C$ : 22.8, 22.6, 19.1, 15.8, 12.2 (5x $CH_3$ ), 45.3, 39.5, 38.1, 37.3, 36.1, 34.7, 30.9, 30.3, 27.6, 25.4, 23.8, 20.3 (12x $CH_2$ ), 60.3, 47.9, 40.3, 38.5 (4xquat.C), 103.1 ( $CH_2=C-$ ), 151.2 ( $CH_2=\underline{C}-$ ), 211.9 ( $\underline{C}=O$ ).

The band at Rf 0.65 gave 87 mg of colourless oil (mixture of three adducts). This material was hydrolyzed with methanolic KOH at room temperature for 1h. Usual work-up gave an oily solid. To this was added ether and the supernatant liquid was pipetted out leaving 21.3 mg of 53b as a colourless crystalline solid mp 183-185°C; exact mass calcd. for  $C_{30}H_{48}O_2$ : 440.3654; found: 440.3657. The ether soluble material (56 mg) was purified by PTLC (64:36 hexane: EtOAc, 4 developments). The band at Rf 0.51 gave 36 mg of a mixture of alcohols 51 and 52 as a colourless viscous oil. The band Rf 0.44 gave 9.8 mg of 53b.

A 50:50 mixture of alcohols (53 mg) 51 and 52 was purified using flash column chromatography on  $SiO_2$  ( $Et_2O$ -petroleum ether, 70:30) to give 10 mg of 51 [mp 143-146°C; IR ( $CHCl_3$ ) 3600-3400, 1705  $cm^{-1}$ ;  $^1H$ mr ( $CDCl_3$ )  $\delta$ : 4.49 (brs, 2H), 3.37 (m, 1H); UV ( $CH_3OH$ )  $\lambda_{max}$  290 nm ( $\epsilon$  96;  $^{13}C$ mr ( $CDCl_3$ )  $\delta_C$ : 22.8, 22.6, 18.8, 13.4, 11.4

(5xCH<sub>3</sub>), 43.0, 39.5, 38.4, 37.6, 36.2, 36.17, 31.3, 29.6, 28.5, 27.3, 25.5, 23.7 (12xCH<sub>2</sub>), 66.6, 54.8, 52.7, 46.2, 35.6, 28.0 (6xCH), 54.8, 53.6, 48.6, 45.6 (4x quat.C), 106.3 (CH<sub>2</sub>=C-), 152.4 (CH<sub>2</sub>=C-), 210.5 (C=O). Exact mass calcd. for C<sub>30</sub>H<sub>48</sub>O<sub>2</sub>: 440.3654; found: 440.3652] together with 36 mg of mixed isomers, and 8 mg of 52 as a colourless viscous oil: IR (CHCl<sub>3</sub>) 3400-3600, 1690 cm<sup>-1</sup>; <sup>1</sup>Hmr (CDCl<sub>3</sub>) δ 5.17 (brs, 1H), 4.93 (m, 1H), 3.04 (m, 1H); UV (CH<sub>3</sub>OH): λ<sub>max</sub> 290 nm (ε 38.5); [α]<sub>D</sub><sup>25</sup> (CHCl<sub>3</sub>) - 23.1; <sup>13</sup>Cmr (CDCl<sub>3</sub>) δ<sub>C</sub>: 22.8, 22.6, 19.0, 15.5, 12.5 (5xCH<sub>3</sub>), 44.7, 44.2, 39.5, 38.4, 37.3, 36.1, 30.9, 30.4, 27.6, 24.8, 23.7, 20.2 (12xCH<sub>2</sub>), 70.2, 57.4, 55.5, 36.3, 35.9, 28.0 (6xCH), 62.3, 50.5, 40.7, 38.7 (4x quat.C), 110.7 (CH<sub>2</sub>=C-), 150.2 (CH<sub>2</sub>=C-), 213.4 (C=O). Exact mass calcd. for C<sub>30</sub>H<sub>48</sub>O<sub>2</sub>: 440.3654; found: 440.3661.

Total of 31 mg of compound 53b obtained above was recrystallized twice from ether giving 24 mg of colourless needles mp 183-185°C. IR(CHCl<sub>3</sub>) 3400-3500, 1710 cm<sup>-1</sup>; <sup>1</sup>Hmr(CDCl<sub>3</sub>) δ 3.52 (m, 1H); <sup>13</sup>Cmr (CDCl<sub>3</sub>) δ<sub>C</sub>: 22.8, 22.6, 19.5, 19.1, 11.7 (5xCH<sub>3</sub>), 49.5, 48.04, 42.5, 41.8, 39.5, 38.1, 36.1, 35.1, 32.1, 26.7, 23.8, 22.1, 19.6 (13xCH<sub>2</sub>), 68.3, 57.9, 55.8, 44.3, 35.7, 28.0 (6xCH), 56.7, 56.6, 49.0, 43.1, 42.5 (5xquat.C), 215.7 (C=O); exact mass calcd. for C<sub>30</sub>H<sub>48</sub>O<sub>2</sub> 440.3654, found 440.3657. <sup>13</sup>Cmr showed it to be 90% pure.

### Acetylation of 53b

The acetate of the above hydroxy ketone 53b was made in a usual manner ( $\text{AC}_2\text{O}$  and pyridine) giving acetoxy ketone 53a as colourless granules: mp  $106-108^\circ\text{C}$  (from  $\text{CH}_3\text{OH}$ ); IR( $\text{CHCl}_3$ )  $1710\text{ cm}^{-1}$ ;  $^1\text{Hmr}$  ( $\text{CDCl}_3$ ) 2.04 (s, 3H), 4.67 (m, 1H); exact mass calcd. for  $\text{C}_{32}\text{H}_{50}\text{O}_3$  482.3759, found 482.3759.  $^{13}\text{Cmr}$  of this compound showed it to be contain -10% impurity.

### Preparation of Steroid diol 53c

To a stirred mixture of 60 mg of lithium aluminium hydride in 10 mL anhydrous ether at room temperature was added a solution of 33 mg of acetoxy ketone 53a in 3.5 mL of anh. ether and the mixture was allowed to stir at room temperature for 2 h. Ice was added and the mixture was neutralised using 5% Aq. HCl. The organic layer was washed with water, dried and concentrated giving 28 mg of an oily solid. The crude product was chromatographed on 10 g  $\text{SiO}_2$  plate (hexane:EtOAc - 76:24, three developments). The band at  $R_f$  0.53 gave 12.8 mg of diol 53c as colourless granules: mp  $154^\circ\text{C}$ . (from petroleum ether-ether, dec.); IR ( $\text{CHCl}_3$ )  $3600, 3400\text{ cm}^{-1}$ ;  $^1\text{Hmr}$  ( $\text{CDCl}_3$ ) 4.18-4.08 (d, J = 6Hz, 1H), 3.6 - 3.46 (m, 2H);  $^{13}\text{Cmr}$  ( $\text{CDCl}_3$ )  $\delta_c$ : 23.1, 22.8, 20.2, 19.4, 13.0 (5x $\text{CH}_3$ ), 54.1, 45.8, 44.1, 43.9, 40.3, 39.0, 36.8, 36.5, 33.2, 30.6, 24.5, 23.7, 21.7 (13x $\text{CH}_2$ ), 72.5, 68.4, 61.4, 57.5, 45.3, 36.7, 28.7 (7xCH), 54.6, 51.8, 47.6, 47.1, 42.8 (5x quat. C); exact mass

calcd. for  $C_{30}H_{50}O_2$  442.3811, obsd. 442.3798.

4b.3.1a Photocycloaddition of  $3\beta$ -acetoxy- $\Delta^{8,9}$ -cholesten-7-one (48a) to allene

A solution of 48a (50 mg) and allene in methylene chloride was irradiated at  $-78^\circ\text{C}$  in the front of a 450W medium pressure Hg lamp. Forty milligrams of crude irradiation product was chromatographed on a 10 g silica plate developed using hexanes:ether - 80:20, five developments. The band at  $R_f$  0.72 gave 5.8 mg of colourless solid. TLC indicated this to be a 80:20 mixture of compounds 49a and 50. IR( $\text{CHCl}_3$ )  $\nu_{\text{max}}$   $1770\text{ cm}^{-1}$  (cyclobutanone). No attempt was made to purify this.

The band at  $R_f$  0.70 gave 15 mg of solid. One recrystallization from ether-methanol gave 9.8 mg of  $\alpha$ -adduct 49a as colourless granules: mp  $117-118^\circ\text{C}$  (lit<sup>71</sup>  $119.5-120.5^\circ\text{C}$ ) IR ( $\text{CHCl}_3$ )  $1720, 1690\text{ cm}^{-1}$ . The band at  $R_f$  0.58 gave 3.2 mg of colourless oil. Hydrolysis ( $\text{KOH} + \text{CH}_3\text{OH}$ ) of this gave previously unreported hydroxy,<sup>71</sup> ketone 53b IR( $\text{CHCl}_3$ ):  $\nu_{\text{max}}$   $3400-3500, 1710\text{ cm}^{-1}$ .

4b.3.1b Irradiation of  $3\beta$ -acetoxy- $\Delta^{8,9}$ -cholesten-11-one (48b) and allene

A solution of 2 mg of 48b in methylene chloride was irradiated at  $-78^\circ\text{C}$  for 12 hr. TLC and mass spectrum of the crude irradiation product indicated it to be the starting material only.

The above reaction was repeated at room temperature for 9h. TLC (Hexane:ether - 3:1) showed the presence of a minor compound (Rf 0.31) and the starting material (Rf 0.27). No attempt was made to analyze the mixture. Mass spectrum: m/e 482 a.m.u.

#### 4b.3.2 Irradiation of 3 $\beta$ -acetoxy- $\Delta^{8,9}$ -cholesten-11-one (48b) and allene on silica gel.

Irradiation of 48b (3 mg) and allene on 300 mg of silica was performed as described previously. TLC of the reaction mixture indicated it to be mostly starting material Rf 0.27 and an adduct Rf 0.31 (Hexanes:Ether - 3:1). The tlc behaviour was identical with the irradiation of 48b in methylene chloride at room temperature. Mass spectrum: m/e 482 a.m.u. No attempt was made to purify the irradiation product.

#### 4b.4 Irradiation of isophorone (56) and allene on silica gel

Irradiation of 56 (150 mg, 1.08 mmol) and allene on 6 g of silica gave 170 mg of oil. Chromatography of the crude irradiation product by PTLC (eluent: benzene, 4 developments) gave 78 mg of 57a as a colourless oil:  $^1\text{Hmr}$  ( $\text{CDCl}_3$ )  $\delta$  5.0-4.9 (m, 2H), 3.3-3.1 (brs, 1H), 1.3 (s, 3H), 1.12 (s, 3H), 0.85 (s, 3H);  $^{13}\text{Cmr}$  ( $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 30.9, 30.3, 27.7 (3xCH<sub>3</sub>), 59.7 (quat. C), 108.2 (CH<sub>2</sub>=C-), 142.3 (CH<sub>2</sub>=C-), 209.9 (C=O); exact mass calcd. for C<sub>12</sub>H<sub>18</sub>O:



178.1357; found: 178.1362; and 55 mg of 57b as a colourless oil:  $^1\text{Hmr}$  ( $\text{CDCl}_3$ )  $\delta$  4.90-4.78 (m, 2H), 1.4 (s, 3H), 1.0 (s, 6H);  $^{13}\text{Cmr}$  ( $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 30.4, 29.45, 29.3 (3xCH<sub>3</sub>), 47.6 (quat. C), 103.5 ( $\text{CH}_2=\text{C}-$ ), 156.1 ( $\text{CH}_2=\text{C}-$ ), 214.16 (C=O); exact mass calcd. for  $\text{C}_{12}\text{H}_{18}\text{O}$ : 178.1357; found; 178.1357.

#### 4b.5 Irradiation of bicyclo[4.4.0]dec-1(6)-en-one (58) and allene on silica gel

Irradiation of 58 (150 mg, 0.79 mmol) and allene on 5 g of silica gave 140 mg of crude oil. Chromatography of the crude oil gave 60 mg of mixture of photocycloadducts 59a and 59b;  $^{13}\text{C}$  data are collected in Table 3.2; exact mass calcd. for  $\text{C}_{13}\text{H}_{18}\text{O}$ : 190.1357; found: 190.1362; and 7 mg of 59c as a colourless oil. A total of 33.5 mg of this material was collected from several reactions and purified by PTLC (hexane-ethyl acetate, 96:4, 3 developments) to give 20 mg of rearrangement product 59c as an oil: IR ( $\text{CHCl}_3$ )  $\nu_{\text{max}}$  1760  $\text{cm}^{-1}$ ;  $^1\text{Hmr}$  ( $\text{CDCl}_3$ )  $\delta$  3.44 (d,  $J=8$  Hz, 1H) 3.0-2.67 (m,  $J_{\text{AB}} = 18$  Hz,  $J_{\text{AX}} = -2.5$  Hz);  $^{13}\text{Cmr}$   $\delta_{\text{C}}$ : 48.8, 37.6, 30.5, 29.6, 27.7, 25.0, 22.4, 21.6 (8xCH<sub>2</sub>), 69.6, 32.0 (2xCH), 51.0, 45.9 (2x quat. C), 212.6 (C=O); exact mass calcd. for  $\text{C}_{13}\text{H}_{18}\text{O}$  190.1357; found 190.1355; oxime mp 72-82°C; Exact mass calcd. for  $\text{C}_{13}\text{H}_{19}\text{ON}$ : 205.1466; found: 205.1469.

Irradiation of 58 and allene in methylene chloride was performed as described previously and no rearrangement product was detected.

4b.6 Photocycloaddition of cyclohexenone, (34), iso-phorone, (56), bicyclo[4.4.0] dec-1(6)-en-one, (58), bicyclo[3.3.0]- $\Delta^7$ -octen-1-one, (60), 4,5,6,7-tetrahydroindan-1-one, (62), and  $\Delta^8$ -hydrindenone (64).

The photocycloaddition of the enones 34, 56, 58, 60, 62, and 64 in methylene chloride and on silica gel was performed as previously described and products analysed by  $^{13}\text{Cmr}$  (see Table 3.1 and 3.2), and molecular formulae were confirmed by mass spectroscopy, results for which are shown below: mixture of 55a and 55b, exact mass calcd. for  $\text{C}_9\text{H}_{12}\text{O}$ :136.089; found 136.089. 57a and 57b exact mass calcd. for  $\text{C}_{12}\text{H}_{18}\text{O}$ :178.1357; found 178.1362. 59a and 59b exact mass calcd. for  $\text{C}_{13}\text{H}_{18}\text{O}$ :190.1357; found 190.1362. 61a and 61b exact mass calcd. for  $\text{C}_{11}\text{H}_{14}\text{O}$ :162.1044; found 162.1040. 63a and 63b exact mass calcd. for  $\text{C}_{12}\text{H}_{16}\text{O}$  176.1201; found 176.1201. 65a and 65b exact mass calcd. for  $\text{C}_{12}\text{H}_{16}\text{O}$  176.1201; found 176.1200.

## REFERENCES

1. Pauling, L. J. Phys. Chem. 1952, 56, 361.
2. a) Iler, R.K. In "The Chemistry of silica". John Wiley and Sons, New York, 1979: Chapter 6.  
b) Unger, K.K. In "Porous Silica", Journal of Chromatography Library; Elsevier, Amsterdam, 1979, Vol. 16.
3. Kiselev, A.V.; Lygin, V.I. in "Infrared Spectra of Surface Compounds". Keterpress Enterprises: Jerusalem, 1975.
4. a) Sindorf, D.W.; Maciel, G.E. J. Am. Chem. Soc. 1983, 105, 1487.  
b) Macial, G.E.; Sindorf, D.W. J. Am. Chem. Soc. 1980, 102, 7607.
5. Fripiat, J.J.; Uytterhoeven, J. J. Phy. Chem. 1962, 66, 800.
6. Knozinger, H. In "The hydrogen bond-recent developments in theory and experiments" (Ed: Schuster, P.) North-Holland Publ. Co. Amsterdam, 1976.
7. Hair, M.L.; Hertl, W. J. Phy. Chem. 1969, 73, 4269.
8. Boehm, H.P. Adv. in Catalysis. 1966, 16, 179.
9. McClellan, A.L.; Harnsberger, J. Colloid. and Interface Sci., 1967, 23, 577.
10. Avnir, D.; Pfeifer, P. Nouv. J. Chem. 1983, 7, 71.
11. Adamson, A.W. Physical Chemistry of Surfaces. IIIrd Ed., John Wiley and Sons, New York, 1976.
12. Snyder, L.R. J. Phy. Chem. 1963, 67, 2622.

13. Nicholls, C.H.; Leermakers, P.A. Adv. Photochem. 1971, 8, 315.
14. Knozinger, H.; Ratnasamy, P. Calal. Rev. - Sci. Eng. 1978, 17, 31.
15. Peri, J.B.; Hannan, R.B. J. Phy. Chem. 1960, 64, 1526.
16. Breuer, H.D.; Jacob, H. Chem. Phys. Lett. 1980, 73, 172.
17. Kortum, G.K. "Reflectance Spectroscopy", Springer-Verlag, New York, Inc. 1969.
18. Leermakers, P.A.; Thomas, H.T. J. Am. Chem. Soc. 1965, 87, 1620.
19. Griffiths, J.; Hart, H. J. Am. Chem. Soc. 1968, 90, 5296.
20. Grauer, Z.; Daniel, H.; Avnir, D. J. Colloid. and Interface Sci. 1984, 96, 411.
21. a) Engel, P.S.; Bishop, D.J.; Page, M.A. J. Am. Chem. Soc. 1978, 100, 7009.  
b) McBride, J.M. Ibid. 1971, 93, 6302.
22. Leermakers, P.A.; Thomas, H.T.; Weis, L.D.; James, F.C. Ibid. 1966, 88, 5075.
23. Johnston, L.J.; de Mayo, P.; Wong, S.K. J. Org. Chem. 1984, 49, 20.
24. Leermakers, P.A.; Weis, L.D.; Thomas, H.T. J. Am. Chem Soc. 1965, 87, 4403.
25. Avnir, D.; de Mayo, P.; Ono, I. J. Chem. Soc. Chem. Commun. 1982, 1109.

26. Frederick, B.; Johnston, L.J.; de Mayo, P.; Wong, S.K.  
Can. J. Chem. 1984, 62, 403.
27. de Mayo, P.; Nakamura, A.; Tsang, P.W.K.; Wong, S.K.  
J. Am. Chem. Soc. 1982, 104, 6824.
28. Leffler, J.E.; Zupancic, J.J. J. Am. Chem. Soc.  
1980, 102, 259.
29. Leffler, J.E.; Barbas, J.T. J. Am. Chem. Soc. 1981,  
103, 7768.
30. a) Anpo, M.; Wada, T.; Kubokawa, Y. Bull. Chem.  
Soc. Jpn. 1977, 50, 31.  
b) Anpo, M.; Kubokawa, Ibid. 1975, 48, 3085.  
c) Anpo, M.; Wada, T.; Kubokawa, Y. Ibid. 1975,  
48, 2663.
31. Weis, L.D.; Evans, T.R.; Leermakers, P.A. J. Am.  
Chem Soc. 1968, 90, 6109.
32. Evans, T.R.; Toth, A.F.; Leermakers, P.A. J. Am. Chem.  
Soc. 1967, 89, 5060.
33. Hecht, H.G.; Crackel, R.L. J. Photochem. 1981, 15, 263.
34. Hecht, H.G.; Crackel, R.L. J. Photochem. 1978, 9, 33.
35. Moesta, H. Discuss. Faraday Soc. 1974, 58, 244.
36. Otsuka, K.; Fukaya, M.; Morikawa, A. Bull. Chem. Soc.  
Japan, 1978, 51, 367.
37. a) Zawadzki, M.E.; Ellis, A.B. Organometallics 1984,  
3, 244.  
b) Zawadzki, M.E.; Ellis, A.B. J. Org. Chem. 1983,  
48, 3156.
38. a) Aoyama, H.; Miyazaki, K.; Sakamoto, M.; Omote, Y.

Chem. Lett. 1983, 1583.

b) Aoyama, H.; Sakamoto, M.; Kuwabara, K.; Yoshida, K.; Omote, Y. J. Am. Chem. Soc. 1983, 105, 1958.

39. Eden, C.; Shaked, Z. Isr. J. Chem. 1975, 13, 1..
40. Werbin, H.; Strom, E.T. J. Am. Chem. Soc. 1968, 90, 7296.
41. Donati, D.; Fiorenza, M.; Sarti-Fantoni, P. J. Hetero-cyclic Chem. 1979, 16, 253.
42. Bauer, R.K.; Borenstein, R.; de Mayo, P.; Okado, K.; Rafalska, M.; Ware, W.R.; Wu, K.C. J. Am. Chem. Soc. 1982, 104, 4635.
43. de Mayo, P. Pure and Appl. Chem. 1981, 54, 1623.
44. de Mayo, P. Accounts Chem. Res. 1971, 4, 41.
45. Lenz, G.R. Reviews Chem. Intermediates 1981, 4, 369.
46. Bauslaugh, P.G. Synthesis 1970, 287.
47. Baldwin, S.W. In Organic Photochem. 1983, 5, 123.
48. Weedon, A.C. In Synthetic Organic Photochemistry (Ed. W.M. Horspool, in press).
49. Loutfy, R.O.; de Mayo, P. J. Am. Chem. Soc. 1977, 99, 3559.
50. de Mayo, P.; Nicholson, A.A.; Tchir, M.F. Can J. Chem. 1969, 47, 711.
51. Wagner, P.J.; Bucheck, D.J. J. Am. Chem. Soc. 1969, 91, 5090.
52. Corey, E.J.; Bass, J.D.; Mahieu, R.; Mitra, R.B. J. Am. Chem. Soc. 1964, 86, 5570.
53. a) Devaquet, A. Salem, L. Can. J. Chem. 1971, 49, 977

- b) Devaquet, A. J. Am. Chem. Soc. 1972, 94, 5160.
54. a) Epiotis, N.D.; Shaik, S. J. Am. Chem. Soc. 1978, 100, 9.
- b) Shaik, S.S. Ibid. 1979, 101, 3184.
55. Margaretha, P. Tetrahedron, 1973, 29, 1317.
56. a) Bonneau, R. J. Am. Chem. Soc. 1980, 102, 3816.
- b) Schuster, D.I.; Greenberg, M.M.; Nunez, I.M.; Tucker, P.C. J. Org. Chem. 1983, 48, 2615.
57. a) McCullough, J.J.; Chorodyn, H.; Santry, D.P. J. Chem. Soc. Chem. Commun. 1969, 570.
- b) Marsh, G.; Kearns, D.R.; Schaffner, K. J. Am. Chem. Soc. 1971, 93, 3129.
58. a) Swenton, J.S.; Wexler, A. J. Am. Chem. Soc., 1976, 98, 1602.
- b) Berenjian, N.; de Mayo, P.; Sturgeon, M.E.; Sydnies, L.K.; Weedon, A.C., Can. J. Chem. 1982, 60, 425.
- c) Challand, B.D.; de Mayo, P. J. Chem. Soc. Chem. Commun. 1968, 982.
59. Bowman, R.M.; Calvo, C.; McCullough, J.J.; Rasmussen, P.W.; Snyder, F.F. J. Org. Chem. 1972, 37, 2084.
60. Singh, P. J. Org. Chem. 1971, 36, 3334.
61. Agosta, W.C.; Lawrance, W.W. J. Org. Chem. 1970, 35, 3851.
62. White, J.D., Gupta, D.N. J. Am. Chem. Soc. 1966, 88, 5364.
63. Rubin, M.B.; Maymon, T.; Glover, D. Isr. J. Chem.

1970, 8, 717.

64. Lenz, G.R. Tetrahedron 1972, 28, 2195.
65. Sunder-Plassman, P.; Nelson, P.H.; Boyle, P.H.;  
Cruz, A.; Iriarte, J.; Crabbé, P.; Zderic, J.A.;  
Edwards, J.A.; Fried, J.H. J. Org. Chem. 1969, 34,  
3779.
66. Serebryakov, É.P.; Vorontsova, L.G.; Struchkova, M.I.;  
Chizhar, O.S.; Pavlov, V.A.; Vol'pin, I.M. Bull. Acad.  
Sci. USSR. Div. Chim. Sci. 1983, 32, 111.
67. Williams, J.R.; Callahan, J.F. J. Chem. Soc. Chem.  
Commun. 1979, 404.
68. Audenhove, M.V.; Keukeleire, D.D.; Vandewalle, M.  
Tetrahedron Lett. 1980, 1979.
69. Sugihara, Y.; Morokoshi, N.; Murata, I. Tetrahedron  
Lett. 1977, 3887.
70. a) Marini-Bettolo, G.; Sahoo, S.P.; Poulton, G.A.;  
Tsai, T.Y.R.; Wiesner, K. Tetrahedron 1980,  
36, 719.  
b) Wiesner, K. Tetrahedron, 1975, 31, 1655.
71. Blount, J.F.; Gray, G.D.; Atwal, K.S.; Tsai, T.Y.R.;  
Wiesner, K. Tetrahedron Lett. 1980, 21, 4413.
72. a) Hanfin, J.W.; Cohen, E. J. Am. Chem. Soc.  
1969, 91, 4494.  
b) McCullough, J.J.; Kelly, J.M.; Rasmussen, P.W.W.,  
J. Org. Chem. 1969, 34, 2933.  
c) Beckers, D.; Nagler, M.; Gillon, A. J. Org. Chem.  
1983, 48, 2584.



- d) See also ref..47 and 48.
73. Timmons, C.J. In 'Elucidation of Organic Structure by Physical and Chemical Methods' (Ed: Bentley, K.W. and Kirby, G.W.) Vol IV, part I, 1972, 10.
74. a) Getty, R.R.; Kerr, J.A.; Trotoman-Dickenson, A.F.; Davies, E. J. Chem. Soc. (A) 1967, 979.  
b) Meunier, H.G.; Abell, P.I. J. Phys. Chem. 1967, 71, 1430.
75. Agnello, E.J.; Laubach, G.D. J. Am. Chem. Soc. 1960, 82, 4293.
76. Nelson, P.H.; Murphy, J.W.; Edwards, J.A.; Fried, J.H. J. Am. Chem. Soc. 1968, 90, 1307;
77. a) Berkov, B.; Cuellar, L.; Grozemkovsky, R.; Avila, N.V.; Cross, A.D. Proc. Chem. Soc. 1964, 215.  
b) Butenandt, A. Chem. Ber. 1939, 72, 1622.
78. Lenz, G.R. J. Chem. Soc. Chem. Commun. 1982, 803.
79. Wexler, A.J.; Hyatt, J.A.; Reynolds, P.W.; Cottrell, C.; Swenton, J.S. J. Am. Chem. Soc. 1978, 100, 512.
80. Cargill, R.L.; Morton, G.H.; Bordner, J. J. Org. Chem. 1980, 45, 3929.
81. Wiesner, K. Cited by Cargill, R.L. ref. 80, footnote 12.
82. Ohfuné, Y.; Shirahama, H.; Matsumoto. Tetrahedron Lett. 1975, 4377.
83. Cargill, R.L.; Bryson, T.A.; Krueger, L.M.; Kempf, J.V.; McKenzie, T.C.; Bordner, J. J. Org. Chem. 1976, 41, 4096.

84. Yates, P.; Loutfy, R.O. Accounts Chem. Res. 1975, 8, 209.
85. Baldwin, S.W.; Page, E.G. J. Chem. Soc. Chem. Commun. 1972, 1337.
86. Still, W.C.; Kahn, M.; Mitra, A. J. Org. Chem. 1978, 43, 2923.
87. Patt, S.L.; Shoolery, J.N. J. Mag. Reson. 1982, 46, 535.
88. Morris, G.A.; Freeman, R.A. J. Am. Chem. Soc. 1979, 101, 760.
89. Fieser, L.F. J. Am. Chem. Soc. 1953, 75, 4395.
90. Patterson, D.G.; Djerassi, C.; Yuh, Y.; Allinger, N. J. Org. Chem. 1977, 42, 2365.
91. Kulkarni, S.B.; Dev, S. Tetrahedron 1968, 24, 553.

Part B: Towards the Total Synthesis of Illudinine.

## CHAPTER 5

### An approach to the synthesis of Illudinine

#### INTRODUCTION

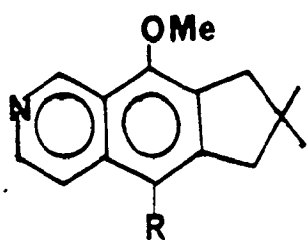
##### 5.1 Isolation and occurrence

Illudinine, 1a, Illudoic acid, 2, Illudacetalic acid, 3, and Illudalic acid, 4, are a group of structurally related fungal metabolites which have been isolated from the culture liquids of Basidiomycete (a major class of true fungi) Clitocybe illudens.<sup>1,2</sup> The Basidiomycotina provide a rich and varied source of sesquiterpenoids, which have been reviewed recently.<sup>3</sup> The Jack-O'-Lantern mushroom (Clitocybe illudens), so called because of its bioluminescent property, is found in large clusters in the late summer in the eastern United States.

Illudinine, 1a, was obtained from the strain of Clitocybe illudens selected for the enhanced production of illudalic acid, 4. In time this strain apparently mutated and instead of 4 it produced a new compound illudinine, 1a.<sup>1</sup>

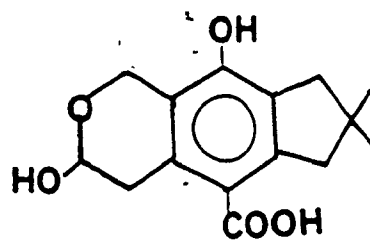
##### 5.2 Classification

Natural products have been classified into families. One of these families, the alkaloids, refers to compounds which are usually found in plants, which possess, in many cases, physiological activity, and whose main characteristic is the presence of a basic nitrogen atom in

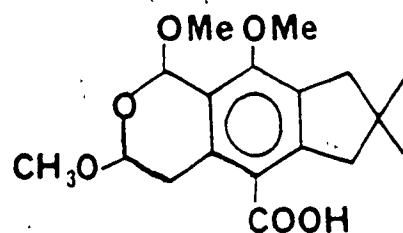


1a R = -COOH

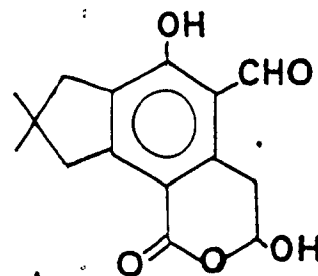
1b = -CH<sub>2</sub>OH



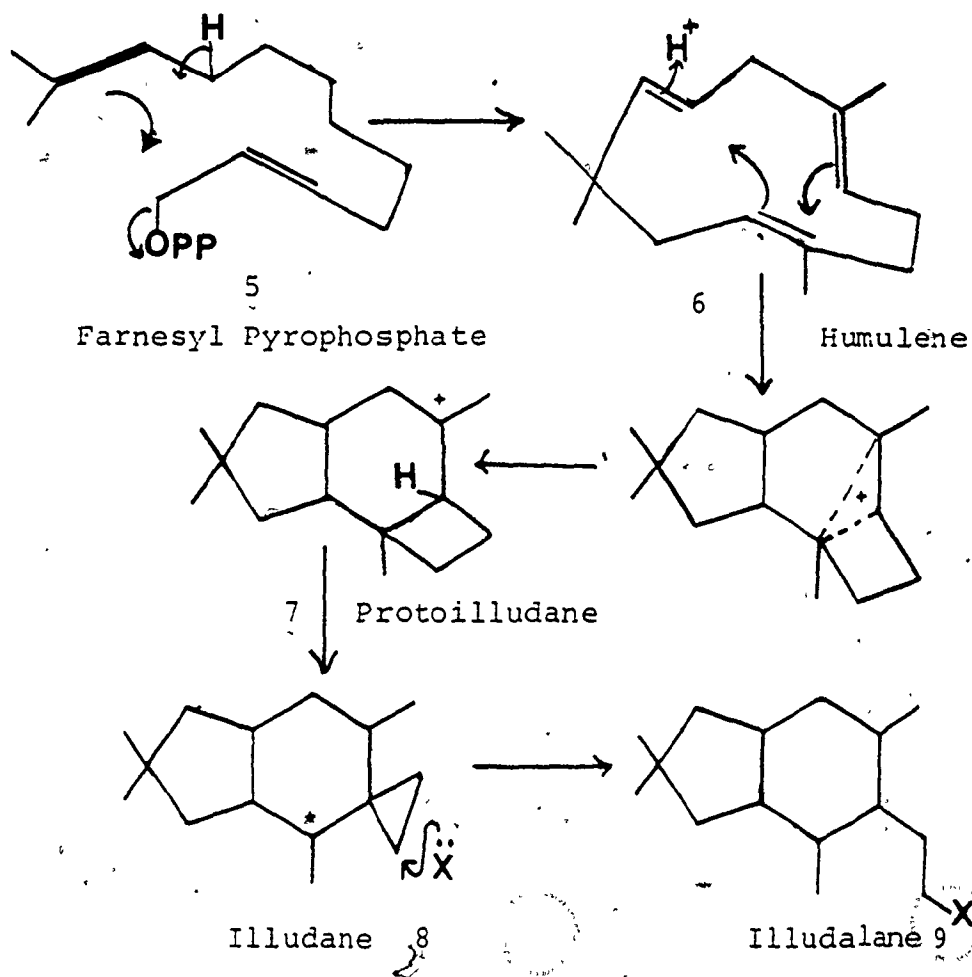
2



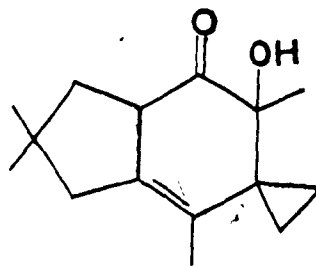
3



4



Scheme I



10

their structure. The systematic classification of these alkaloids is nearly impossible. However, the acceptable practice is to regroup them on the basis of either carbon-nitrogen skeleton or their natural sources.

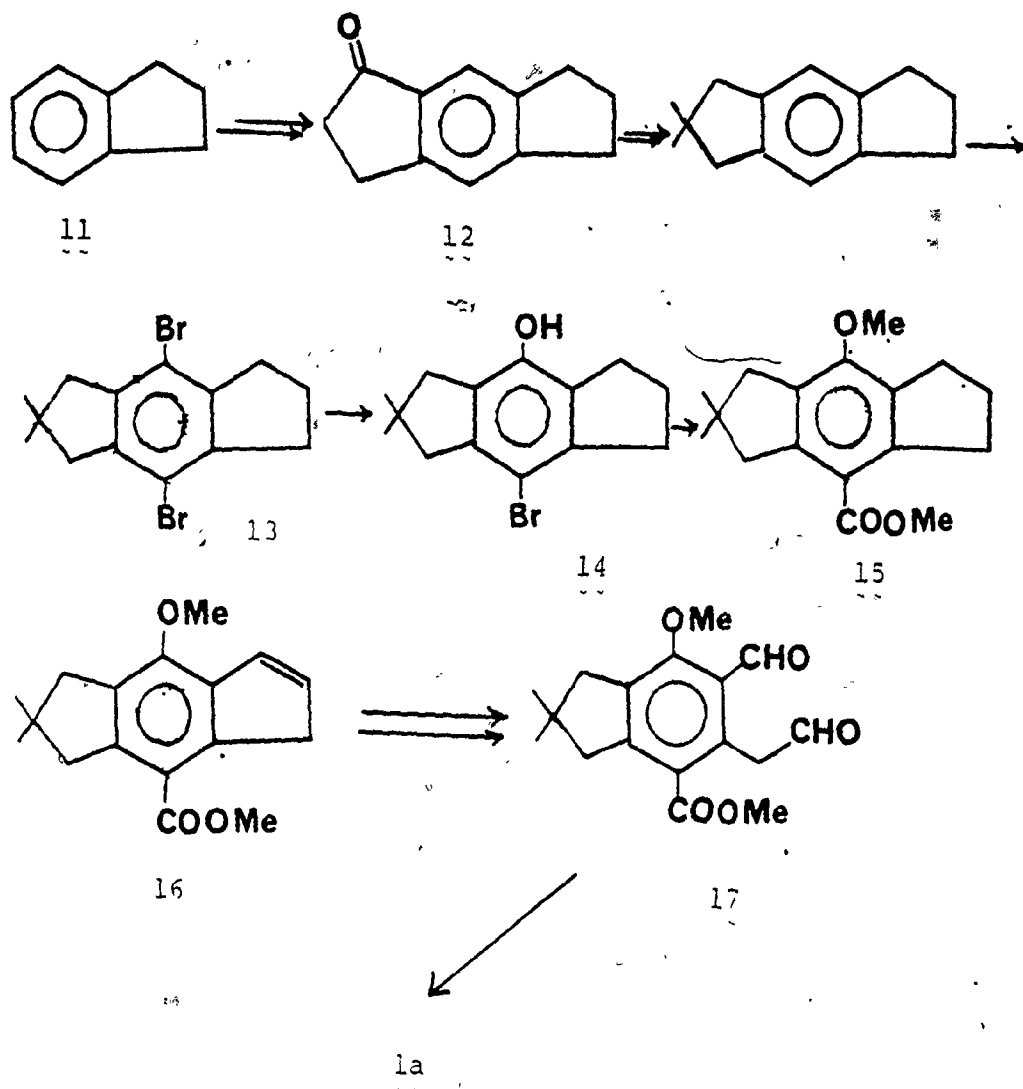
Illudinine, 1a, has been classified as a 'Sesquiterpenoid Alkaloid'.<sup>4</sup>

### 5.3 Biosynthesis of Illudinine

Illudacetic acid, 3, a metabolite produced by another strain of the same species is readily converted to illudinine, 1a, by treatment with ammonia.<sup>2</sup> It was suggested, based upon the observation that 3 was no longer isolated from the culture that produced illudinine 1a, that it might be derived biogenetically from the protoilludane skeleton 7 via illudacetic acid, 3. The biogenesis of the illudlanes 9 has not been investigated; a hypothetical pathway proposed by Ayer is shown in scheme I.<sup>3</sup> Humulene 6, which arises by cyclization of farnesyl pyrophosphate 5, can be further cyclized to the protoilludane skeleton 7. Bond cleavage of illudane 8 results in the formation of illudalane skeleton 9. Hanson has studied the biosynthesis of illudin M 10 and it was found to be in agreement with the hypothetical route proposed by Ayer.<sup>3</sup>

### 5.4 Structural Studies

The structure of illudinine was determined by spectroscopic (<sup>1</sup>Hmr, I.R., UV) and chemical methods. <sup>1</sup>Hmr



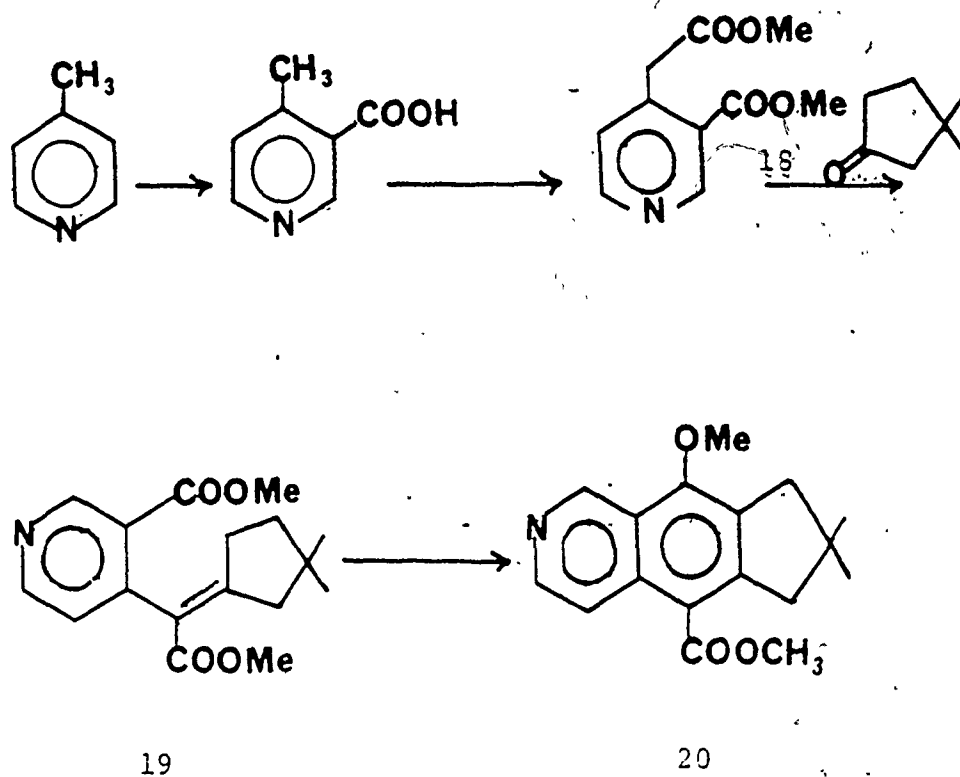
Scheme II



showed signals at  $\delta$  8.27 (1H, d), 8.35 (1H, d), 9.4 (1H, s) characteristic of the isoquinoline nucleus. The presence of two methylene signals at  $\delta$  3.13 and  $\delta$  3.09 and two methyl signals at  $\delta$  1.17 suggested the presence of a gem-dimethylcyclopentane fused to the benzene ring. The reaction of 1a with diazomethane resulted in the formation of methyl-demethylilludinate 20, which was reduced with lithium aluminium hydride to give the primary alcohol derivative of illudinine, 1b. The formation of the alcohol 1b from 20 indicated the presence of a carbonyl group. A molecular ion peak was observed at m/e 271 for 1a.

#### 5.5 Woodward's total synthesis of Illudinine, 1a

The total synthesis of Illudinine 1a was achieved by Woodward (Scheme II).<sup>6</sup> Friedel-Crafts acylation of indane, 11, with  $\beta$ -chloropropionylchloride followed by acid catalyzed cyclization gave both the linear and nonlinear hydrindacenone. The desired isomer 12 was alkylated and then subjected to Clemmensen reduction. Bromination of the resultant hydrocarbon gave the dibromide 13 and its treatment with *n*-Buli gave an aryl carbanion which was transformed to phenol 14. The phenolic hydroxyl group was protected, the Grignard reagent was formed and reacted with methylchloroformate to give the methoxyester 15. Selective oxidation, reduction and dehydration gave olefin 16, which was transformed to dialdehyde 17, using osmium tetroxide-sodium metaperiodate. Illudinine, 1a, was



Scheme III

prepared by treating 17 with ammonia.

#### 5.6 Wenkert's total synthesis of Methyl-demethyl--illudinate, 20

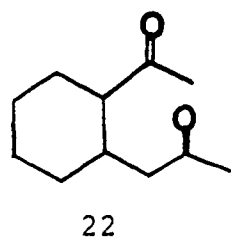
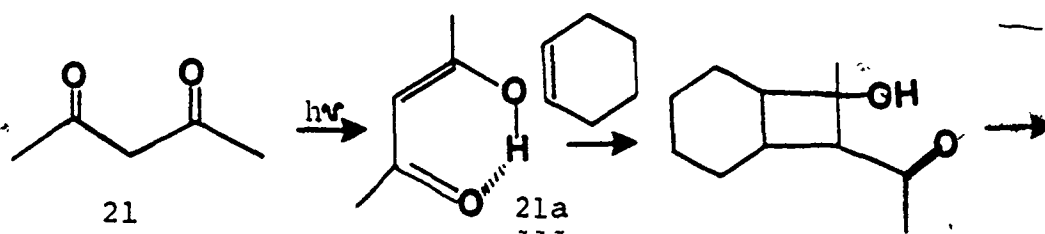
Methyl-demethylilludinate, 20, a derivative of illudinine was prepared from  $\gamma$ -picoline by Wenkert (Scheme III).<sup>7</sup> The key step in the synthesis involved the base catalyzed condensation of methyl 4-carbomethoxy--methylnicotinate with 3,3-dimethylcyclopentanone 18. Esterification of the resultant acid ester derivative yielded a mixture of the diester derivative 19 and its stereoisomer. Their further base treatment under equilibrium conditions gave 20 as the exclusive product.

#### 5.7 Fungal metabolites as targets in Organic Synthesis

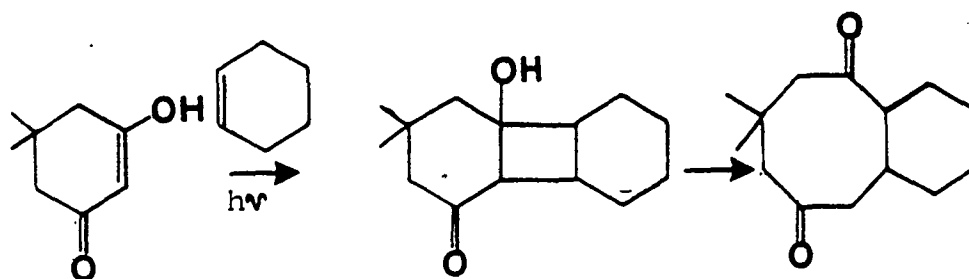
The chemical syntheses of these fungal metabolites are rendered challenging by the diversity of the functional groups which flank their aromatic nuclei. These compounds possess highly pronounced physiological properties, which encouraged us to attempt an alternative, and shorter, photochemical approach to Illudinine.

#### 5.8 The de Mayo Reaction

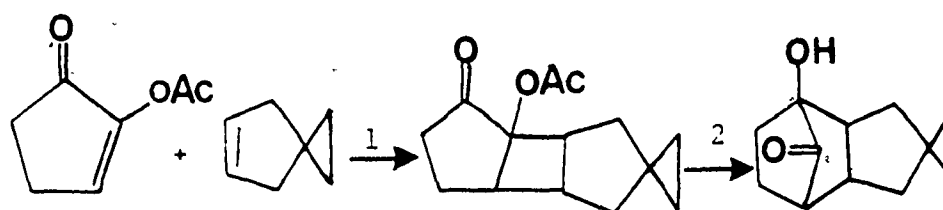
The photochemical addition of alkenes to enolized 1,2 or 1,3 diketones and their derivatives is referred to as the "de Mayo Reaction". The synthetic aspects of the de Mayo reaction have been extensively reviewed.<sup>8a</sup> A recent



Scheme IV



Scheme V

1 =  $h\nu$ 

2 = Base

Scheme VI

updated review by Weedon is in press.<sup>8b</sup> As the bulk of the subject has been extensively reviewed this short introduction will be restricted to the applications of de Mayo reaction in the synthesis of natural products.

#### 5.8.1 Acyclic 1,3 diketone

Irradiation of acyclic 1,3 diketones such as 2,4 pentadione, 21, in the presence of an alkene (Scheme IV) results in the formation of an acyl cyclobutanol as the primary photoadduct, which undergoes a retroaldol reaction to give the 1,5 diketone 22.<sup>9</sup> The rate of energy-wasting cis-trans isomerization of the photoexcited enol is presumably reduced by intramolecular hydrogen bonding between the ketone and the enol (21a). Unsymmetrical acyclic  $\beta$ -diketones can enolize in two directions and the possibility of two photochemically active enol tautomers also arises. Photochemical cycloadditions frequently occur preferentially from a single enol, even though both forms may be present. A recent report indicates that the products of the addition of cyclohexene and cyclopentene to benzoylacetone are derived largely from the form which is enolized towards the aromatic ring.<sup>10</sup> Efficient photochemical syntheses of valerane, isovalerane<sup>11</sup> and loganin<sup>12</sup> have been achieved by irradiating suitable acyclic 1,3 diketones in the presence of alkenes.

### 5.8.2 Cyclic 1,3-diketone

The de Mayo reaction also occurs with cyclic 1,3 diones, the enol forms of which also behave as  $\beta$ -hydroxyenones. The diones possess a saturated carbonyl chromophore at 290 nm, the enol forms have an intense  $\pi \rightarrow \pi^*$  band at 250 nm. Irradiation of the enol band in the presence of alkenes results in photocycloaddition to give a cyclobutanol as a primary photoproduct, which undergoes retroaldolization to give for instance, a cyclooctanedione (Scheme V). This reaction has been used to synthesize  $\gamma$ -tropolone,<sup>13</sup> stipitonic acid,<sup>14</sup> and hirsutene.<sup>15</sup>

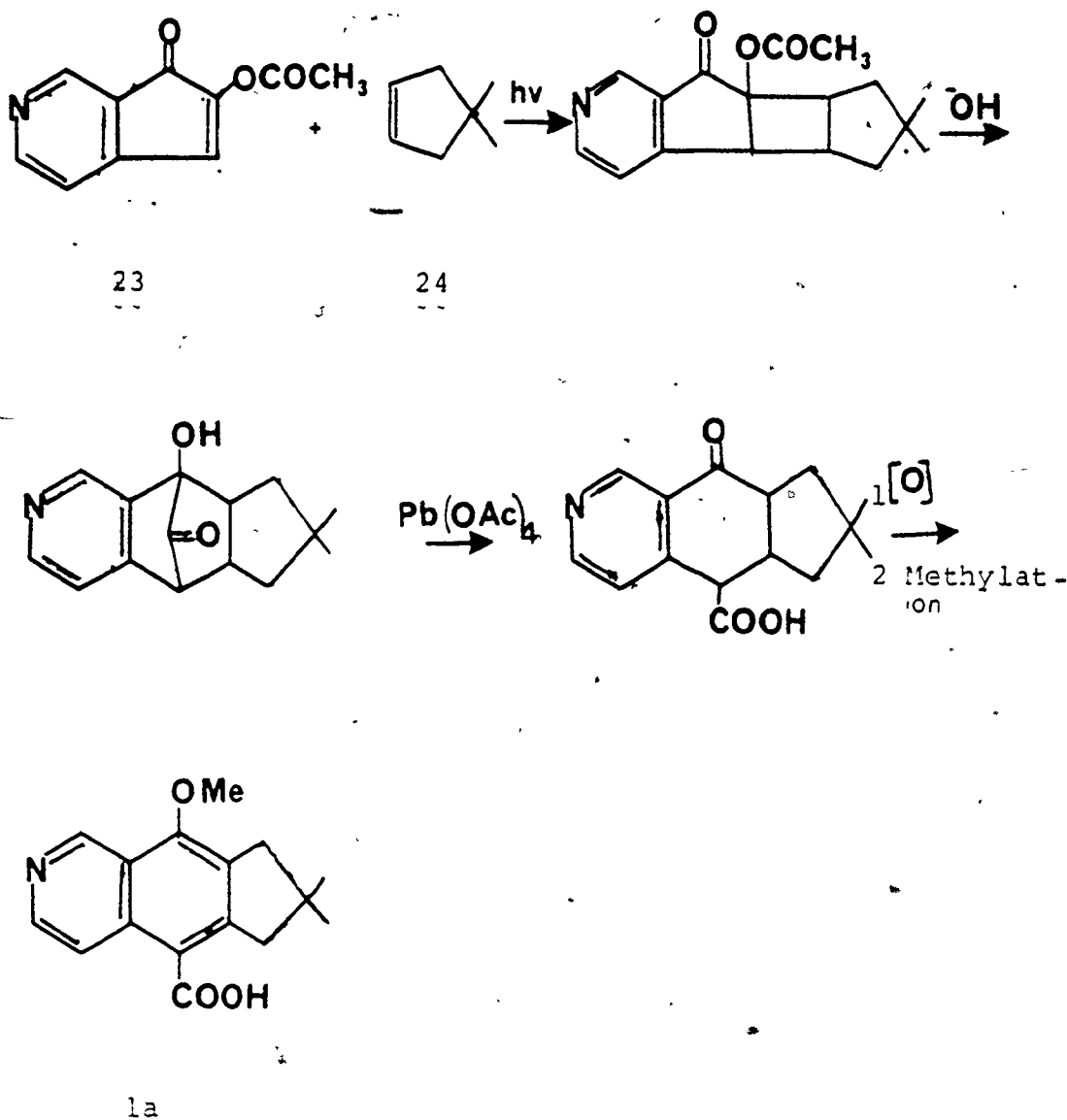
### 5.8.3 Intramolecular Additions

The intramolecular de Mayo reaction has been used recently to synthesize  $\Delta^{8,9}$  capnellane<sup>16</sup> and  $\pm$ -zizaene.<sup>17</sup>

### 5.8.4 Cyclic 1,2-diones

Photochemical cycloaddition to enolized 1,2-cyclohexadione do not proceed;<sup>8b</sup> like other 2-substituted cyclohexenones it is inert when irradiated with alkenes.<sup>9</sup> However, enolized cyclopentane-1,2-diones do undergo the de Mayo reaction (Scheme VI) and this strategy has been used to synthesize methyl isomarasmate<sup>18</sup> and acorenone.<sup>19</sup> A key step in these syntheses is the base catalyzed rearrangement of the photoadduct following deacylation to a bicyclo[2.2.1] heptane system, which can be cleaved with  $\text{Pb}(\text{OAc})_4$  to a 4-carboxycyclohexanone.

## SYNTHETIC PLAN



Scheme VII

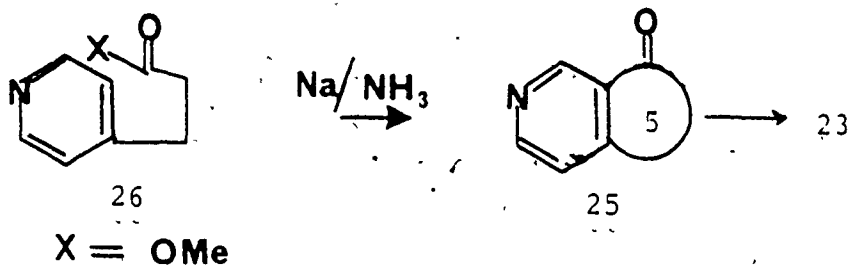
### 5.8.5 Photochemical approach to illudinine, 1a

The planned synthesis of illudinine, 1a, involved the photocycloaddition of the enolized cyclopentane-1,2-dione derivative 23 to the known 3,3-dimethylcyclopentene, 24 to give the cyclobutane derivative as a primary photoproduct (Scheme VII). Base-catalyzed rearrangement of the resulting cyclobutane adduct could then give a bicyclo[2.2.1] heptane system which could be cleaved with lead tetra-acetate to furnish the 4-carboxycyclohexanone derivative. The 4-carboxycyclohexanone derivative can undergo aromatization and selective methylation to give Illudinine 1a. The synthesis of the natural product 1a therefore involves the synthesis of precursors 23 and 24.

## RESULTS AND DISCUSSION

### 5.9 An approach to the synthesis of 5,6-dihydro-2--pyrindin-7-one, 25 via regioselective metalation of pyridine

The literature synthesis<sup>20</sup> of 5,6-dihydro-2-pyrindin-7-one, 25, a precursor of 23 is long and tedious. It was decided to attempt the synthesis of the heterocycle 25 by an alternative method.



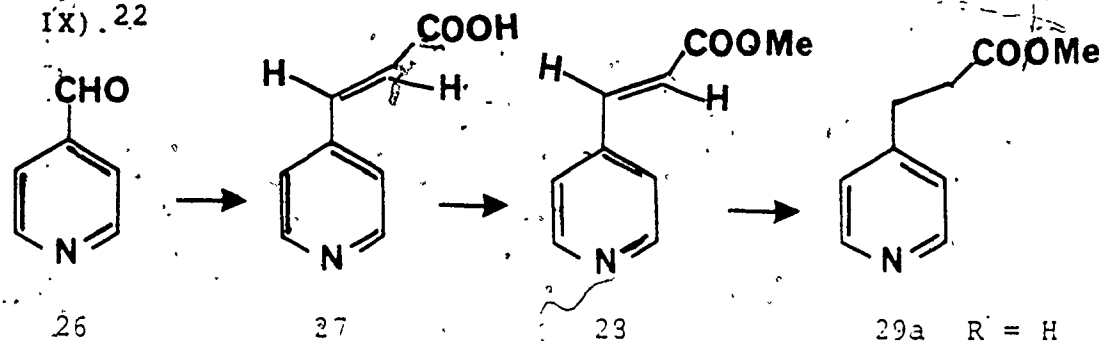
Scheme VIII



The synthesis of 5,6-dihydro-2-pyridin-7-one, 25, from 26 (as shown in Scheme VIII) requires generation of a carbanion at position 3 of the pyridine ring using sodium in liq. ammonia, and intramolecular condensation with a suitable side chain. The generation of a carbanion at the  $\beta$ -position of pyridine and its alkylation with alkyl bromide in the presence of sodium in liquid ammonia has been reported.<sup>21</sup>

#### 5.9.1 Synthesis of methyl ( $\beta$ -4-pyridyl)propionate, 29b

The reported synthetic route for the preparation of methyl  $\beta$ -4(pyridyl) propionate, 29b, was followed (Scheme IX).<sup>22</sup>



Scheme IX

29b R = CH<sub>3</sub>

Condensation of pyridine 4-carboxaldehyde, 26, with malonic acid by the literature procedure<sup>22</sup> gave

$\beta$ -(4-pyridyl)-acrylic acid, 27. Crystallization gave a sample with melting point in good agreement with the literature value. The <sup>1</sup>Hmr spectrum of this compound,

previously not reported, exhibited doublets (J = 18 Hz) at  $\delta$  6.5-6.3 and  $\delta$  7.1-7.3 integrating to one proton

each, attributed to the olefinic hydrogens of the side chain

of 27. Also present were the signals due to pyridine protons at  $\delta$  8.4-8.0 and  $\delta$  7.7-7.4, as doublets ( $J = -5$  Hz) integrating to two protons each. The mass spectrum possessed the correct molecular ion at 149 mass units.

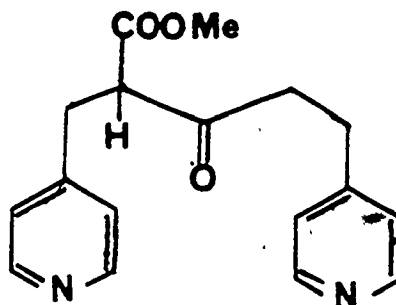
Hydrogenation of the pyridyl acrylic acid, 27 in water with  $PtO_2$  as described in the literature<sup>22</sup> was attempted; however, reduction was extremely slow mainly due to the insolubility of 27. The hydrogenation was also tried in methanol and ethyl acetate, but it gave only 10% conversion to 29a in methanol and very slow conversion in ethyl acetate. Consequently, the insoluble acid 27 was converted to its sodium salt and then hydrogenated over  $PtO_2$  to give pyridyl-propionic acid 29a. The  $^1H$ mr spectrum of this compound exhibited a multiplet centred at  $\delta$  2.9 integrating to four protons which was attributed to the methylene hydrogens of the side chain. The mass spectrum possessed the correct molecular ion at 151 mass units. In this procedure only 56% yield was obtained. Consequently, 27 was converted to methyl( $\beta$ -4-pyridyl) acrylate 28, with methanol and sulfuric acid, in 96% yield. In the  $^1H$ mr spectrum of 28 doublets ( $J = 18$  Hz) at  $\delta$  7.9-7.6 and 6.8-6.0 were seen, integrating to a single proton each, which were assigned to the olefinic hydrogens of the side chain. The presence of pyridine protons was revealed by two doublets ( $J = -5$  Hz) at  $\delta$  8.85-8.7 and  $\delta$  7.55-7.4 integrating to two protons each. The methyl group of ester 28 appeared as a singlet at  $\delta$  4.0. The mass spectrum

possessed the correct molecular ion at 163 a.m.u.

Methyl( $\beta$ -4-pyridyl)acrylate, 28, was hydrogenated in methanol over  $\text{PtO}_2$  to give methyl( $\beta$ -4-pyridyl) propionate, 29b, in 100% yield. The carbonyl absorption in the I.R. spectrum was seen at  $1745\text{ cm}^{-1}$ . The  $^1\text{Hmr}$  spectrum showed a multiplet centred at  $\delta$  2.8 integrating to four hydrogens which was assigned to the methylene hydrogens of the ester side chain. The methyl group of the ester in 29b appeared as a singlet at  $\delta$  3.9. The mass spectrum possessed the correct mass ion at 165 a.m.u.

#### 5.9.2 Attempted synthesis of 5,6-dihydro-2-pyridin-7-one, 25.

By analogy with the alkylation of pyridine reported in the literature,<sup>21</sup> methyl( $\beta$ -4-pyridyl) propionate, 29b, would be expected to cyclize to give the 5,6-dihydro-2-pyridin-7-one, 25. When a solution of 29b in dry tetrahydrofuran was added to a blue coloured solution of sodium in liquid ammonia, the blue colour discharged immediately. After an acidic work-up, t.l.c. showed the presence of a compound slightly more polar than the starting material 29b. Purification of the crude product using preparative t.l.c. gave 31% of the polar compound. No cyclized product was detected.

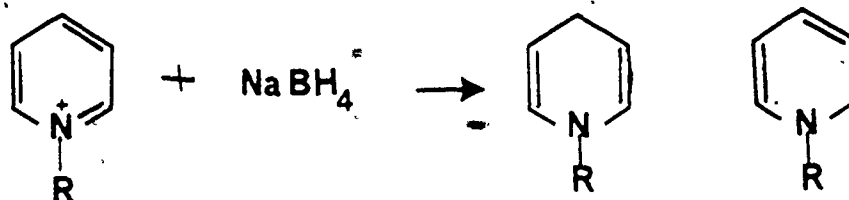


30

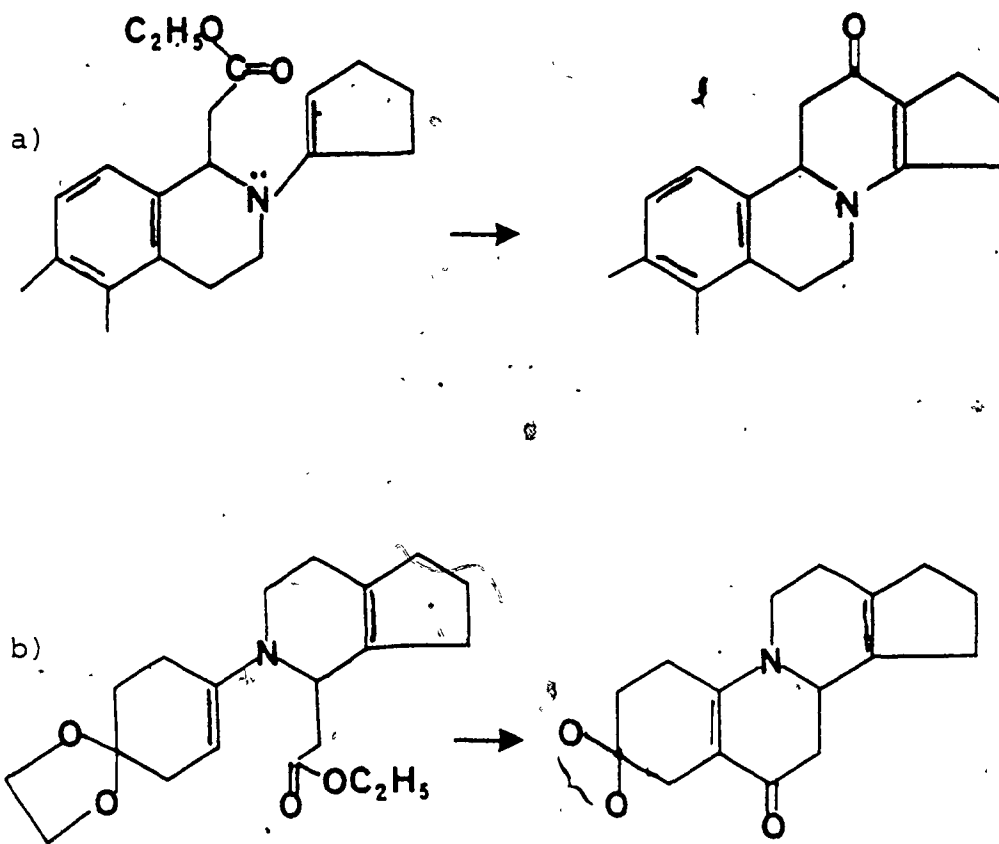
### 5.9.3 Identification of 30

The assignment of structure 30 to the more polar product was made on the basis of the  $^1\text{Hmr}$ , I.R. and mass spectra. The I.R. spectrum ( $\nu$  1720, 1750  $\text{cm}^{-1}$ ) showed the presence of a  $\beta$ -ketoester. The  $^1\text{Hmr}$  spectrum showed the presence of eight aromatic protons. The methyl group of the ester appeared as a singlet at  $\delta$ 4.1 and the two methylene and methine protons, adjacent to the keto-ester moiety, had moved downfield to  $\delta$ 3.4 and  $\delta$ 4.1, respectively, as a result of the keto-ester functionality. The mass spectrum possessed the correct molecular ion at 298 mass units.

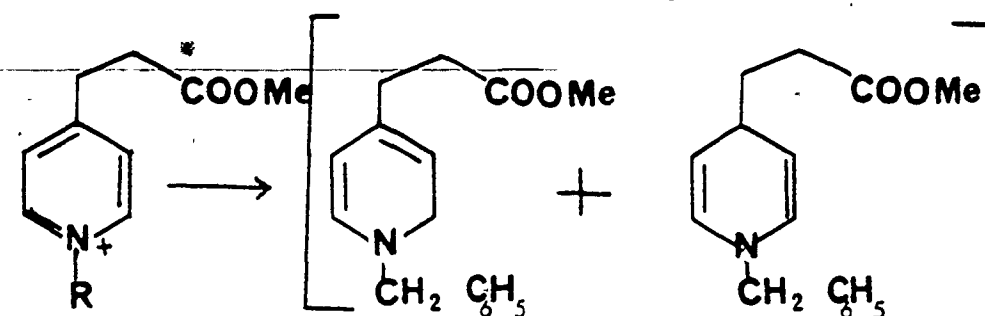
The structure of dipyriddy  $\beta$ -ketoester, 30 was further confirmed by its independent synthesis from methyl( $\beta$ -4-pyridyl)propionate, 29b. Claisen condensation of 29b was carried out with sodium-methoxide in refluxing benzene. After work-up and preparative t.l.c. 47% of the dipyriddy  $\beta$ -ketoester 30 was obtained. The  $^1\text{Hmr}$ , I.R. and mass.



Scheme X



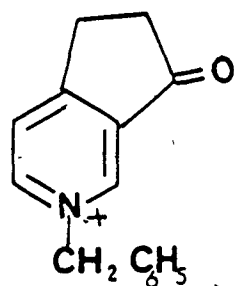
Scheme XI



31a  $\text{R} = \text{CH}_2\text{C}_6\text{H}_5$

32

31b  $\text{R} = \text{C}(=\text{O})_3$



25

Scheme XII

spectra of 30 were found to be identical with the polar compound isolated from the reaction of methyl( $\beta$ -4--pyridyl)propionate, 29b, in sodium and liq ammonia.

The failure of methyl( $\beta$ -4 pyridyl) propionate 29b to cyclize indicated that deprotonation of the methylene protons adjacent to the carbonyl group of the ester was faster compared to deprotonation of the pyridine ring.

Following the failure of the attempted cyclization of methyl( $\beta$ -4 pyridyl) propionate 29b to 5,6-dihydro-2--pyridin-7-one, 25, an alternative method of cyclization was investigated.

#### 5.10 Attempted synthesis of 25 by an intramolecular acylation of enamine

By analogy with the reduction of *n*-alkyl pyridinium salts to dihydropyridines (Scheme X) and the intramolecular cyclization of enamines (Scheme XI), the following synthetic route was proposed (see Scheme XII).

##### 5.10.1 Synthesis of N-benzyl pyridinium methyl propionate

Methyl ( $\beta$ -4-pyridyl)propionate 29b was reacted with benzylbromide in ethyl acetate to give the bromide salt of N-benzyl pyridinium methyl propionate 31a; however, the product, being very hygroscopic, could not be crystallized. The I.R. spectrum ( $1730\text{ cm}^{-1}$ ) showed the presence of an ester functionality. The  $^1\text{Hmr}$  spectrum of this compound exhibited a multiplet centred at  $\delta 7.8$

integrating to five protons which was attributed to the aromatic protons of the benzyl group. The presence of the benzyl protons of the pyridinium salt was revealed by a singlet at  $\delta$ 6.5. The  $\alpha$  protons of the pyridinium salt moved downfield to  $\delta$ 9.5 as a result of the positive charge on nitrogen. The mass spectrum possessed the expected molecular ion at 255 a.m.u.

#### 5.10.2 Reduction of the pyridinium salt, 31a

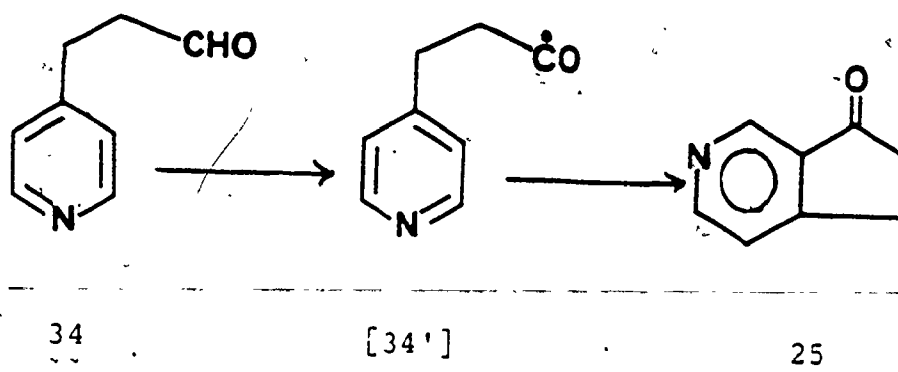
The reduction of pyridinium salt 31a by sodium borohydride in alkaline aqueous solution was carried out using the procedure of Büchi.<sup>26</sup> The <sup>1</sup>Hmr spectrum of the product did not contain any pyridine protons. Five aromatic protons were observed as a singlet at  $\delta$ 7.2 compared with the aromatic benzene protons absorbing between  $\delta$ 8.0-7.4 (multiplet) in the starting material. The presence of a methyl group in the ester was revealed by a singlet at  $\delta$ -4.0. The presence of multiplets at  $\delta$ 6.1, 4.7 and 4.1 was attributed to the protons of the dihydropyridine nucleus.

#### 5.10.3 Attempted cyclization of dihydropyridine esters

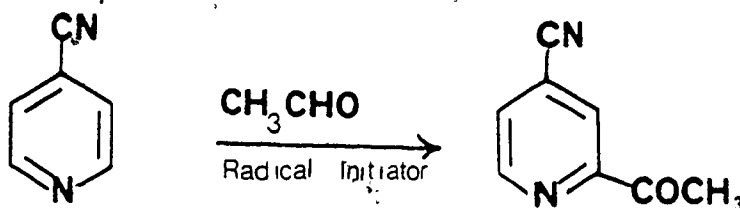
Cyclization of dihydropyridine ester 32 was attempted using the procedure of Meyers based on the enamine acylation (see Scheme XI, example a).<sup>22</sup> The compound 32 was refluxed in toluene in the presence of trifluoroacetic acid for 30 h. T.L.C. of the crude product after work-up



failed to show a positive DNP test, and the presence of an ester group was revealed by the I.R. spectrum.



Scheme XIII



Scheme XIV

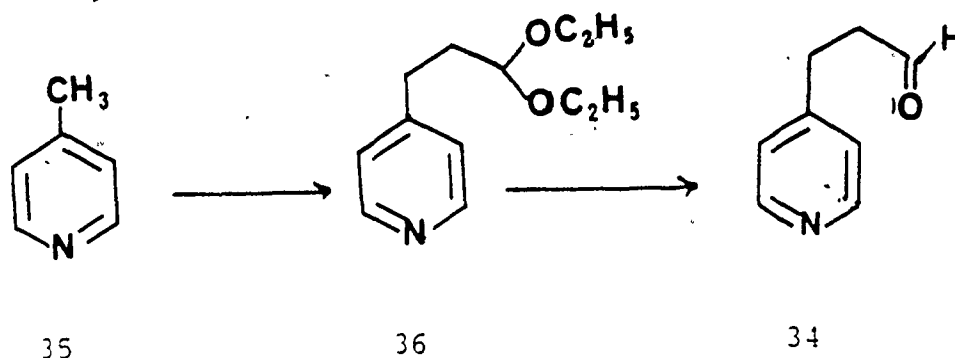
#### 5.11 Strategy for the synthesis of 25 based on the homolytic acylation of pyridine

Following the failure of the cyclization of methyl $\beta$ -(4-pyridyl)propionate, 29b, to the desired cyclized product 25, the alternative route shown in Scheme XIII was considered. The synthesis of 5,6-dihydro-2-pyrindin-7-one, 25 from 3-(4-pyridyl)propionaldehyde, 34 would require generation of an acyl radical using radical initiator followed by an intramolecular acylation of [34'].

Homolytic acylation of pyridines is known to give mostly the 2 and 4 acyl substituted compounds (Scheme XIV).<sup>27</sup> It was thought that intramolecular homolytic acylation of 4-pyridyl-propionaldehyde, 34, where the  $\gamma$  position is blocked and  $\alpha$  position is inaccessible, might result in  $\beta$  acylation to give the desired cyclized product 25.

#### 5.11.1 Synthesis of 4-Pyridyl-propionaldehyde

The following synthetic route for the synthesis of 4-pyridyl-propionaldehyde, 34 was followed (Scheme XV).



Scheme XV

$\gamma$ -Picoline 35 was treated with *n*-Buli and the resulting anion (4-picolylolithium) was alkylated with bromoacetaldehyde diethylacetal to give 4-pyridyl-acetaldehyde diethyl acetal 36 in 88% yield. In the <sup>1</sup>Hmr spectrum 36 showed a triplet (*J* = 6Hz) at  $\delta$ 4.5 integrating to a single proton which was assigned to the methine proton. The presence of pyridine protons was revealed by two doublets (*J* = -5Hz) at  $\delta$ 8.4 and 7.3 integrating to two protons each.

The mass spectrum possessed the correct molecular ion at 209 mass units. After the preparation of 36, its hydrolysis of the diethyl acetal group with dil. HCl was carried out. In the I.R. spectrum a strong band appeared at  $1715\text{ cm}^{-1}$  corresponding to an aldehyde function. The proton n.m.r. spectrum of this compound exhibited a singlet at  $\delta 9.5$  consistent with the new aldehyde proton. The mass spectrum contained the expected molecular ion at 135 a.m.u.

#### 5.11.2 Attempted cyclization of 4-pyridyl-propionaldehyde

Cyclization of 4-pyridyl-propionaldehyde, 34, to the desired cyclized ketone 25 was attempted using the procedure of Caronna<sup>27</sup> based on homolytic acylation of protonated pyridines. The compound 34 was treated with *t*-butylhydroperoxide and sulfuric acid followed by a solution of  $\text{FeSO}_4$ . After work-up, tlc and the I.R. spectrum revealed that only the unreacted aldehyde 34 was present.

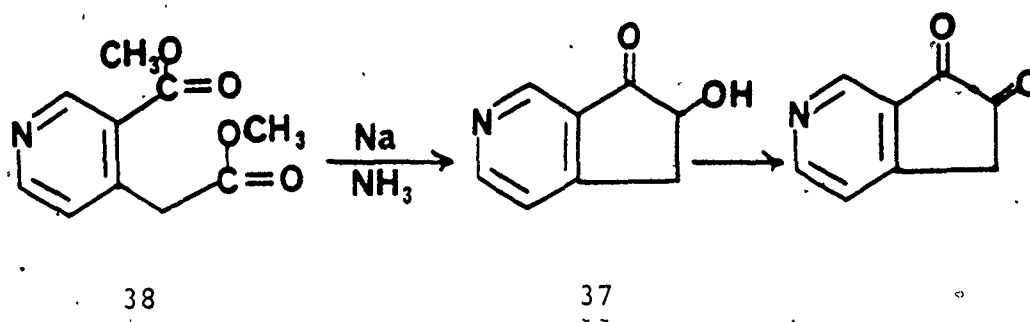
Since no net reaction with *t*-butylhydroperoxide and ferrous sulphate was observed another radical initiator, di-*t*-butyl peroxide was tried. It was hoped that reaction of compound 34 with di-*t*-butylperoxide would give the acyl radical and this radical would undergo acylation to give the desired heterocyclic ketone 25. After reaction of this reagent with 34 for 2h, t.l.c. and the  $^1\text{Hmr}$  spectrum of the crude product showed 60% loss of the aldehyde function, but also the absence of the cyclization product 25. Prolonged

heating of the mixture of aldehyde 34 and peroxide resulted in apparent polymerization.

It has been found<sup>27</sup> that attack by radicals at position 3 of pyridines predominates only if the attacking radical has a higher than an average amount of electrophilic character; otherwise position 2 of the pyridine is the most reactive towards radical attack. The failure of 4-pyridyl-propionaldehyde, 34, to cyclize in the presence of a radical initiator can be attributed to the inability of the pyridine nucleus to undergo intramolecular attack by acyl radical at position 3. The loss of the carbonyl function and formation of polymer can be considered to occur via loss of carbon monoxide followed by further side reactions of the resulting alkyl radical.

#### 5.12 Synthetic approach to indanone derivative 37 via acyloin condensation of 38

Following the failure of the cyclization product formation from methyl $\beta$ (4 pyridyl) propionate, 29b and the aldehyde derivative 34, an alternate synthetic route involving the hydroxy ketone 37 was considered (Scheme XVI). The synthesis of cyclized hydroxyketone 37 involves the preparation of  $\gamma$ -homocinchomeric acid dimethyl ester 38. The reported synthesis of 38 (Scheme III) is long (9 steps) and results in a low yield; consequently an alternative, shorter route was sought.



Scheme XVI

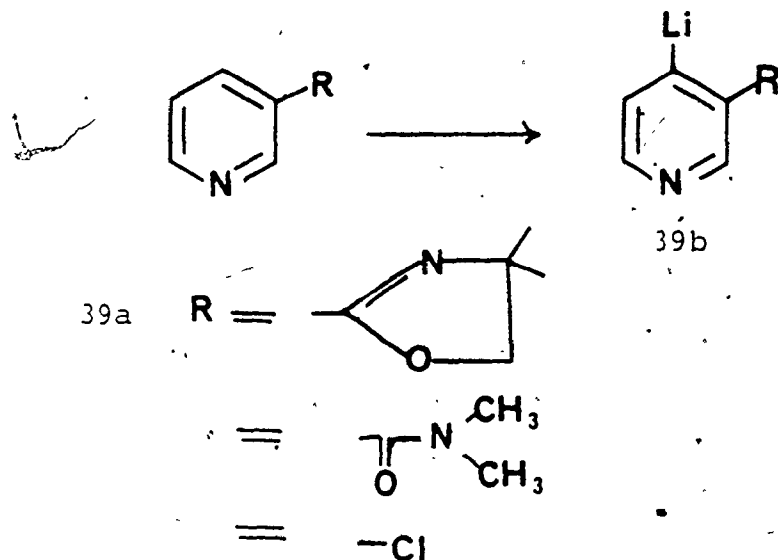
### 5.13 Synthesis of $\gamma$ -homocinchomeric acid dimethyl ester,

#### 38

#### 5.13.1 Heteroatom facilitated lithiation of pyridines

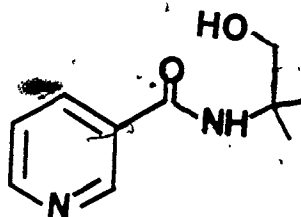
For the envisaged route to 38, it was desired to generate selectively a carbanion at position 4 of a nicotinic acid derivative and alkylate with a suitable reagent to give the desired product. Meyers has recently shown that 3-pyridyloxazoline can be regiospecifically metalated at position 4 when treated with lithium 2,2,6,6-tetramethyl-piperidide (LTMP).<sup>28</sup> The directing oxazoline group is a protected form of an acid, and it can easily be transformed to an ester group by treatment with dil.HCl, evaporation to dryness, and treatment with diazomethane. Beta(ortho) lithiation consists in the replacement of an  $sp^2$ -carbon bound hydrogen atom by lithium at the position beta to a functional group attached to carbocyclic aromatic system. It is assumed that the initial step in this reaction is the coordination of the metalating agent with the lone pair of the azomethine bond. The nearest

available proton in the ortho position then suffers a protophilic attack, leading to an internally chelated organolithium species. Oxazolines,<sup>28</sup> *t*-amides<sup>29</sup> and halides<sup>31</sup> are known to be powerful functional groups for ortholithiations. This is due to their high capacity for effective coordination with the lithiating agent via the nonbonding pair of electrons of their  $sp^2$ -hybridized nitrogen atoms, and the ability to acidify adjacent hydrogens through their electron withdrawing properties.<sup>30</sup> In fact, the directing ability of oxazolines and *sec*-amides is so high that it can over-ride nucleophilic attack on the azomethine bond of pyridine by the metalating agents (organolithium).



3-Pyridyl- $\Delta^2$ -oxazoline,<sup>28a</sup> 3-pyridyl-amide<sup>29</sup> and 3-pyridyl-chloride<sup>31</sup> have been shown to undergo regiospecific metalation at position 4 of pyridine in the presence of a suitable metalating organolithium reagent (cf. 39).





39

The I.R. spectrum of this compound exhibited a strong band at  $1680\text{ cm}^{-1}$  indicating the presence of an amide group. The  $^1\text{Hmr}$  spectrum of the solid amide exhibited singlets at  $\delta 6.7$  and  $4.7$  integrating to one proton each, which were assigned to an amide and hydroxyl group respectively. This solid amide was treated with thionyl chloride to give 39a. The  $^1\text{Hmr}$  spectrum of this compound showed singlets at  $\delta 4.0$  and  $\delta 1.33$ , which were assigned to the methylene and gem-dimethyl protons of the  $\Delta^2$ -oxazoline. In the I.R. spectrum a strong band appeared at  $1640\text{ cm}^{-1}$  corresponding to the oxazoline function. The mass spectrum contained the expected molecular ion at 176 mass units. Later, a reported procedure (1982) for the synthesis of 39a was followed.<sup>28a</sup>

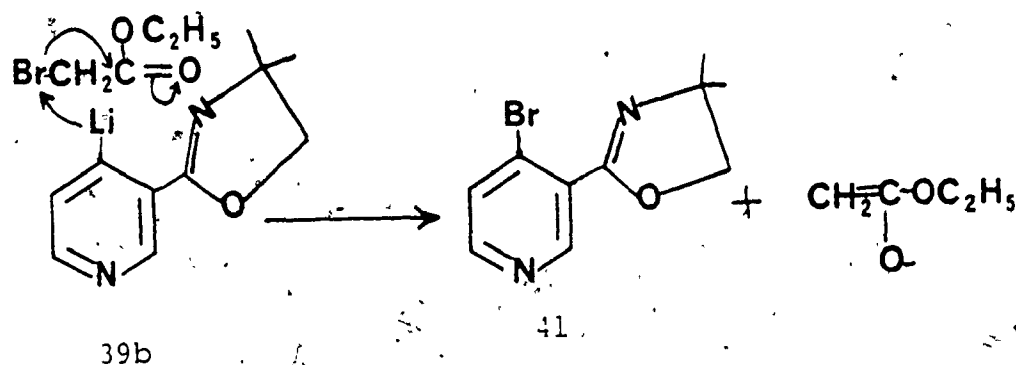
2-(3-Pyridyl)-4,4-dimethyl- $\Delta^2$ -oxazoline 39a was prepared in 52.4% yield from nicotinic acid chloride hydrochloride and 2-amino-2-methyl-1-propanol by the procedure of Meyers.<sup>28a</sup>



### 5.15 Alkylation of 4-lithio derivative

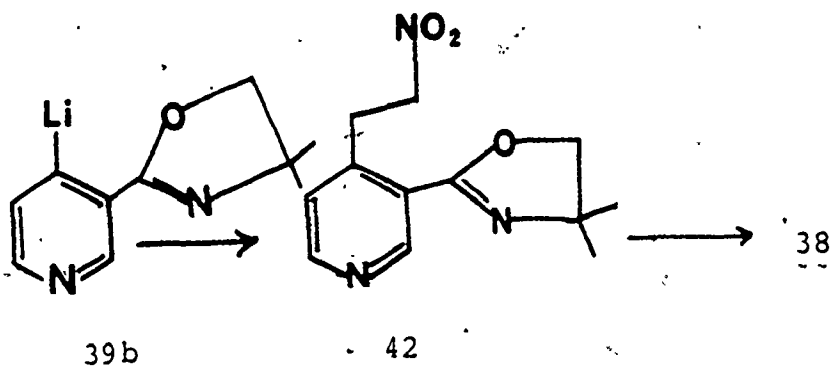
Addition of lithium 2,2,6,6-tetramethyl-piperidide (LiTMP) to 39a (THF, 0°C) gave the desired 4-lithio derivative 39b which on treatment with ethyl bromoacetate, furnished a viscous oil. T.L.C. indicated the presence of starting material and the formation of a product less polar than starting material. This less polar compound was isolated by preparative t.l.c. in 27% yield. The  $^1\text{Hmr}$  spectrum of the less polar reaction product exhibited the absence of the  $\gamma$ -proton of the 3-pyridyl-oxazoline 39a which suggested that alkylation had taken place regiospecifically at the 4-position of 2-(3

Pyridyl)-4,4-dimethyl- $\Delta^2$ -oxazoline 39a. The absence of signals other than those seen for 39a suggested that the C<sub>4</sub> position was bonded to a halogen atom. Mass spectroscopy (molecular ion at 254 a.m.u.) suggested the presence of 41.



Scheme XVIII

The mechanism of formation of compound 41 may reasonably be regarded as proceeding via attack on electrophilic bromine followed by elimination of an ester enolate (Scheme XVIII).



Scheme XIX

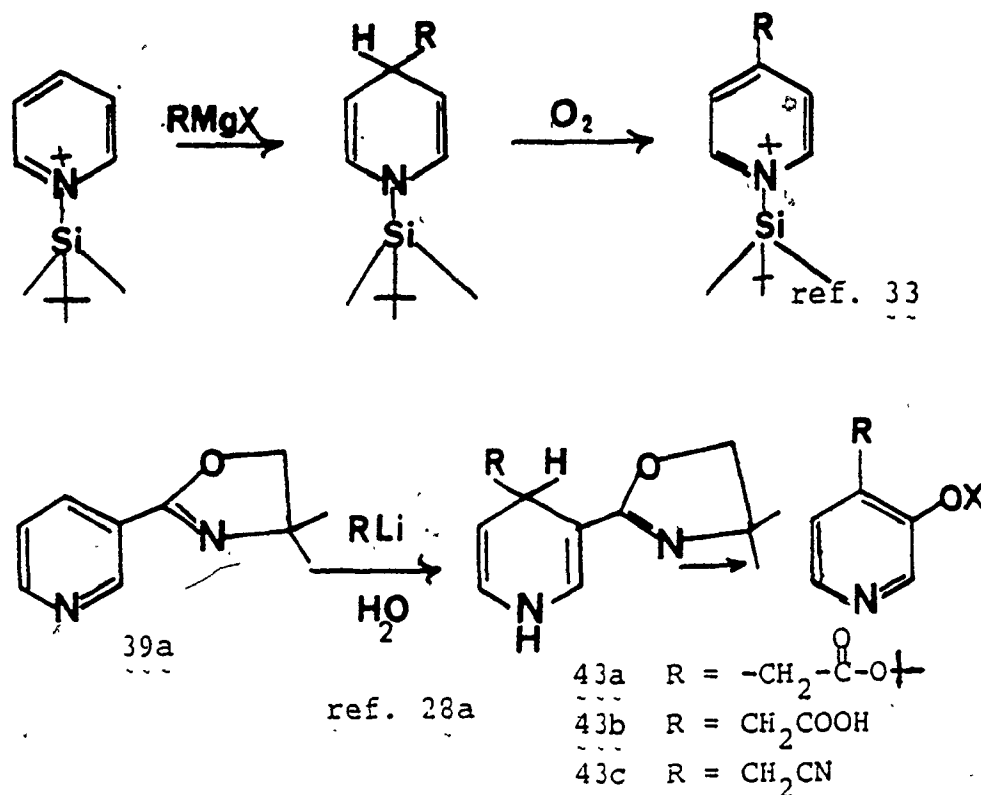
5.16' Approach to the synthesis of 38 via addition of oxazoline stabilized carbanion to a Michael acceptor

Following the failure of the 4-lithiopyridine 39b to alkylate with ethylbromoacetate to give the desired product 40, an alternative reagent was considered. It was thought that Michael addition of 4-Lithiopyridine 39b to nitroethylene might result in the formation of nitroethane derivative 42 which could be easily converted to the desired  $\gamma$ -homocinchomeric acid dimethyl ester 38 (Scheme XIX). Nitroethylene has been shown to undergo Michael addition with enamines.<sup>32</sup> This reagent was prepared by the literature procedure.<sup>32</sup> 4-lithiopyridine 39b was treated with one equivalent of nitroethylene in benzene solution, and two compounds were isolated following preparative t.l.c. The less polar of the two showed in the <sup>1</sup>Hmr spectrum the expected nitroethane signals in 42 at  $\delta$ 5.8-4.5 (triplet) and  $\delta$ 3.7-3.4 (triplet). The I.R. spectrum of this compound exhibited a strong band at 1560 cm<sup>-1</sup>.

indicating the presence of the nitro group. The less polar product from the reaction of 4-lithiopyridine 39b with nitroethylene was obtained as a colourless liquid which became yellow on standing. The I.R. spectrum of this compound exhibited a strong band at  $1560\text{ cm}^{-1}$  indicating the presence of a nitro group. The intensity of the nitro stretching band at  $1560\text{ cm}^{-1}$  was two times stronger than observed in 42, which suggested the presence of an additional nitro group. The structure of this undesired product could not be deduced from the spectral data available to us. The yield of this product increased drastically when excess nitroethylene was used. This product might have formed from the initially formed monoadduct anion which could undergo Michael addition with a second nitroethylene unit. The desired product was obtained in 10% yield. Several repetitions of the reaction, under carefully dried conditions gave the same results.

#### 5.17 Regiospecific nucleophilic addition to pyridines

Organolithium addition to pyridines has been known since 1930. Recently, many reports involving regiospecific nucleophilic addition at the 4-position of pyridine have appeared. Silylated pyridines have been shown to undergo regiospecific nucleophilic addition at the  $\gamma$  position in quantitative yield.<sup>33</sup>



Scheme XX

Meyers has recently shown<sup>28a</sup> that the oxazoline moiety in 2-(3-Pyridyl)-4,4-dimethyl- $\Delta^2$ -oxazoline, 39a through its coordination with organolithium and Grignard reagents, leads to very high yields of 4-substituted, 1,4-dihydro pyridines which are readily oxidized to 4-substituted pyridines (Scheme XX). The single exception to the above scheme was reported using *t*-butyllithium which gave the  $\alpha$ -substituted, 1,4dihydropyridine.<sup>28a</sup>

### 5.18 Synthetic approach via regiospecific addition of a monoanion of ester to pyridyl oxazoline

With this synthetic route in mind the nucleophilic addition of the enolate of *t*-butylacetate to 3-pyridyl oxazoline 39a was attempted, but it gave back the starting material. By analogy with the regiospecific addition reported by Meyers, it was thought that the addition of an ester enolate to 3-pyridyl oxazoline 39a might result in the formation of 43a ( $R-CH_2-\overset{O}{\overset{||}{C}}-O-$ ). The failure to observe any nucleophilic addition product 43a can be attributed to the poor nucleophilicity of ester enolates as compared to organolithium reagents.

### 5.19 Synthetic approach via addition of dianion of acetic acid to 3-pyridyl oxazoline

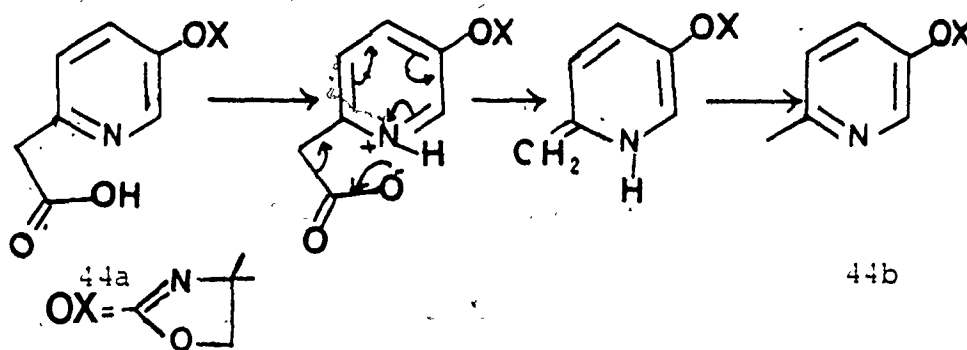
Since no net reaction with ester enolate was observed a stronger nucleophile, the dianion of acetic acid, was tried. It was hoped that reaction of this nucleophile with

39a would give the 1,4 dihydropyridine 43b ( $R-CH_2-\overset{O}{\overset{||}{C}}-OH$ ).

When the 3-pyridyl oxazoline 39a was treated with 1.1 equivalents of the dianion of acetic acid under anhydrous conditions, the t.l.c. of the crude reaction mixture after usual work-up indicated the presence of a major amount of starting material in addition to two new compounds.

Isolation of the two new compounds was performed by preparative t.l.c. The I.R. spectrum of the less polar of the two was very similar to that of the starting oxazoline

the two was very similar to that of the starting oxazoline 39a and the  $^1\text{Hmr}$  spectrum exhibited the absence of one  $\alpha$  proton of 3-pyridyl oxazoline 39a at  $-\delta 8.0$ , which suggested that alkylation had taken place at the 2-position of 3-pyridyloxazoline 39a. In the  $^1\text{Hmr}$  spectrum of this compound the presence of a singlet at  $\delta 2.5$  integrating to 3 protons suggested the presence of a methyl group. Meyers has pointed out that the addition of bulkier organolithium reagents occurs at the more accessible carbon adjacent to the pyridine nitrogen.<sup>28a</sup> By analogy with the exceptions reported by Meyers, the addition of the dianion of acetic acid followed by oxidation would give the picolinic acid derivative 44a. 2-Picolinic acid has been known to undergo

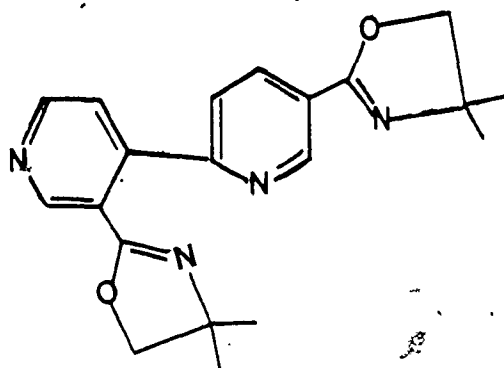


Scheme XXI

decarboxylation very readily.<sup>34</sup> Thus the formation of 2 picoline derivative 44b from 44a can be regarded as proceeding via the mechanism shown in Scheme XXI.

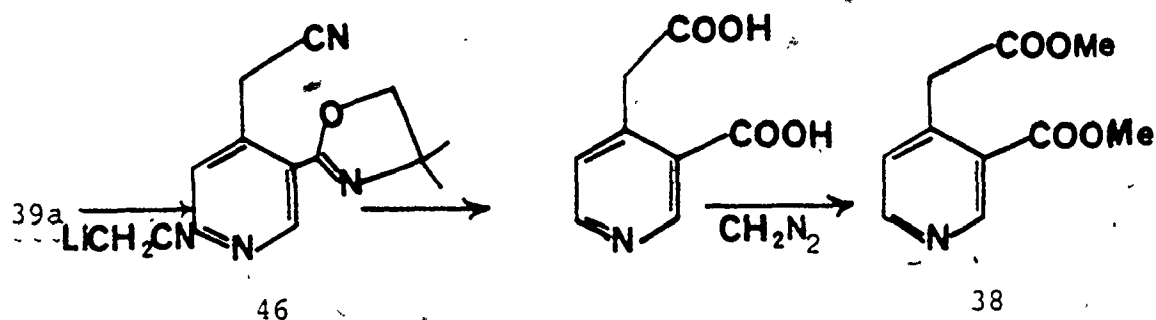
### 5.19.1 Identification of 45

The  $^1\text{Hmr}$  spectrum of the less polar compound showed the presence of 6 aromatic protons as compared with 4 aromatic protons in the starting material. The methylene groups of the oxazoline appeared as two singlets at  $\delta$ 4.3 and 4.1 and the gemdimethyl groups were seen as two singlets integrating to 6 hydrogens each. The mass spectrum of the new substance appeared to exhibit a molecular ion at 350 mass units. The mass spectrum and the  $^1\text{Hmr}$  spectrum suggested the presence of two pyridyloxazolines 39a linked together. The formation of 3-pyridyl oxazolines 39a linked



45

to each other can be considered as proceeding via attack of 4-lithiopyridine 39b on 39a followed by air oxidation to give a dimer, or some radical mechanism may be operative. The assignment of the tentative structure 45 to the less polar compound is based on  $^1\text{Hmr}$  and mass spectral evidence only.



Scheme XXII

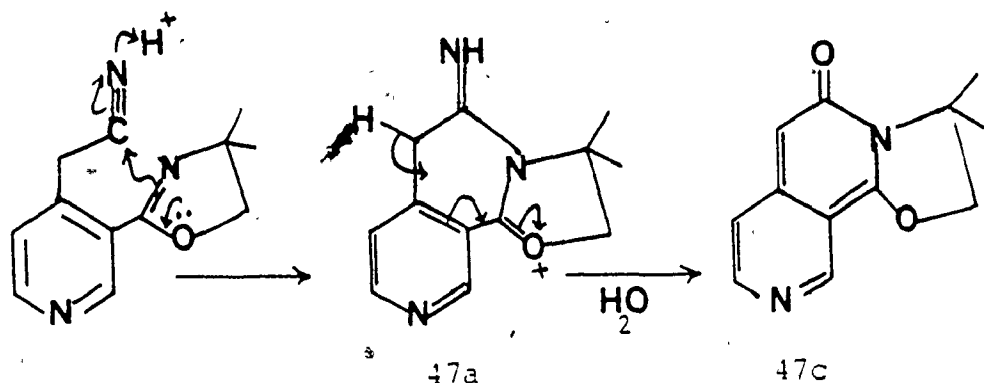
5.20 Synthetic approach via addition of monoanion of nitrile to 3-pyridyl oxazoline

Following the failure of the addition of nucleophiles to give the desired product in one step, the addition of lithioacetonitrile by the literature procedure gave the 1,4-dihydropyridine **43c** ( $\text{R}=\text{CH}_2\text{CN}$ ).<sup>28a</sup> The resulting 1,4-dihydropyridyl- $\Delta^2$ -oxazoline derivative **43c** was oxidized with chloranil to give 4-picolyl nitrile **46**. The <sup>1</sup>Hmr spectrum of this compound showed a singlet at  $\delta 4.3$  which was assigned to the methylene group of the new side chain. It was thought that the hydrolysis of **46** followed by treatment with diazomethane would give the desired product **38** (Scheme XXII).



### 5.20.1 Attempted acidic hydrolysis of 4-picolyl nitrile derivative

By analogy with the published procedure for the hydrolysis of 3-picolyl nitrile,<sup>35</sup> the acidic hydrolysis of 4-picolyl nitrile derivative 46 was carried out. When after 20 h the reaction mixture was worked-up, t.l.c. indicated the absence of the starting material and the formation of a less polar product. The IR spectrum of the product indicated the loss of the oxazoline function stretching vibration at  $1650\text{ cm}^{-1}$ . In addition two very strong bands appeared at  $1635$  and  $1680\text{ cm}^{-1}$ . The mass spectrum of this compound showed a molecular ion at 216 mass units which indicated the presence of an even number of nitrogen atoms. In the  $^1\text{Hmr}$  spectrum no resonance due to the nitrile bonded methylene was visible and a singlet appeared at  $\delta 5.7$ , corresponding to one proton only. The exclusive product from acidic hydrolysis of 46 was assigned structure



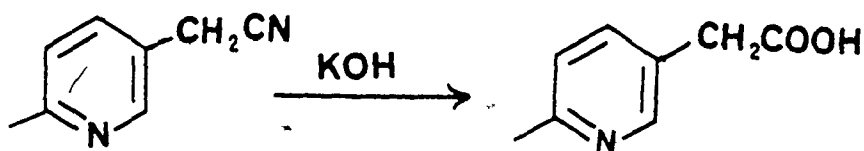
Scheme XXIII

47c. The mechanism for the formation of this unusual product can be considered to proceed via intramolecular nucleophilic attack of oxazoline nitrogen on the nitrile

function to furnish the imine intermediate 47a, which can undergo tautomerization followed by hydrolysis of the imine function to give the heterocyclic lactam 47c, as shown in (Scheme XXIII). Several repetitions of the reaction under different reaction conditions gave the same result.

#### 5.21 Basic hydrolysis of 4-picolyl nitrile derivative

Since no desired compound was obtained from the acidic hydrolysis of 46, basic hydrolysis following a literature procedure,<sup>35</sup> as shown below, was attempted.



When a solution of methanolic potassium hydroxide was refluxed with 46, tlc of aliquots indicated gradual disappearance of starting material and quite clean formation of a less polar product. This product showed identical  $R_f$  to the lactam 47c formed in the reaction of 46 with HCl solution. The reaction mixture was refluxed for 8 h; concentrated to dryness and to it was added an ethereal solution of diazomethane ( $\text{CH}_2\text{N}_2$ ). After work-up, isolation of the two products was performed by preparative t.l.c. The more polar of the two showed I.R. spectrum,  $^1\text{Hmr}$  spectrum and precise mass identical to that of 47c. The less polar product exhibited in the IR spectrum a strong

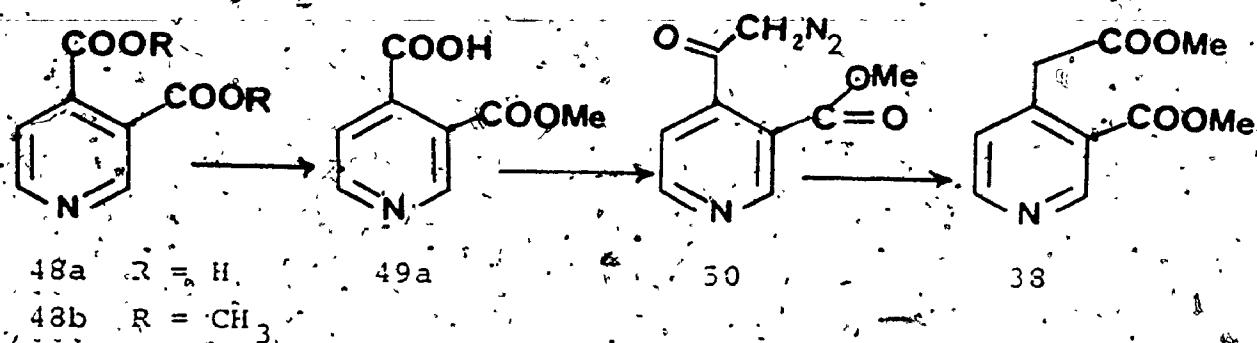
band at  $1725\text{ cm}^{-1}$  suggesting the presence of an ester group. The mass spectrum of this product ( $m/e$  209) revealed that it was the desired  $\gamma$ -homocinchomeronic acid dimethyl ester, 38. The desired product was obtained in only 10% yield. Since the yield of this reaction was poor, variations in the reaction conditions were attempted. Isolation of the lactam 47c from the basic hydrolysis suggested that the 38 was formed from picolyl nitrile derivative, 46, through 47c. The most reasonable route to 38 under basic hydrolysis conditions is via initial formation of an amide followed by intramolecular cyclization to give 47c (Scheme XXIV). The oxazine in 47c ring opens by attack of hydroxide to give oxazoline 47e or imide derivative 47f which undergoes hydrolysis (acid treatment during work-up) and esterification to give 38.

The incomplete hydrolysis of the picolyl nitrile derivative 46 was thought to arise from the fact that the intermediate lactam 47c was resistant to basic hydrolysis. Accordingly, stronger reaction conditions involving hydrolysis in DMSO containing aqueous sodium hydroxide was investigated. This procedure enhanced the formation of 47c; however, no improvement in the hydrolysis of 47c was observed. When the large scale basic hydrolysis ( $\text{CH}_3\text{OH-KOH}$ ) of  $\gamma$ -homocinchomeronic acid dimethyl ester, 38, followed by esterification was carried out difficulties were encountered in purifying the complex mixture of



products obtained, possibly because the pyridine nucleus is prone to attack by strong nucleophiles. This problem was avoided by using 10% KOH in CH<sub>3</sub>OH/H<sub>2</sub>O (V 1/1). When a solution of aqueous KOH was refluxed with 4 picolyl nitrile derivative, 46, tlc of aliquots withdrawn after 4 h indicated disappearance of the starting material and the formation of less polar products. The solution was refluxed for further 27h, until complete disappearance of 47c, before the reaction was worked-up. Esterification and flash chromatography of the yellow oil obtained gave a 39% yield of  $\gamma$ -homo-cinchomeric acid dimethyl ester, 38. The <sup>1</sup>Hmr spectrum of this compound did not contain an oxazoline group. Also absent was the singlet signal present in the cyclized intermediate 47c at  $\delta$ 5.6. The methyl ester groups in 38 resonated as two singlets at 3.6 and 3.8 ppm. The low yield obtained in the reaction can be attributed to the incomplete hydrolysis of 4-picolyl nitrile derivative, 46. No attempts were made to characterise the minor products obtained.

In view of the low yield of diester 38 by the above route an alternative procedure was examined: Scheme XXV.



Scheme XXV

### 5.22 Synthesis and hydrolysis of cinchomeronic dimethyl ester, 48b

Cinchomeronic dimethyl ester 48b was prepared by the literature procedure.<sup>36a</sup> The hydrolysis of cinchomeronic dimethyl ester 48b with one equivalent of 0.53 N methanolic KOH at -10°C was performed by the literature procedure in order to obtain 3-carbomethoxy-nicotinic acid, 49. Contrary to the published report<sup>36a</sup> HPLC analysis showed the presence of four compounds. On t.l.c. the hydrolysis products were more polar than starting material and traveled together in all organic solvents tried and all adsorbents used (silica and alumina). Separation was eventually achieved by using HPLC with the following solvent system: (nBuOH:AcOH:H<sub>2</sub>O; (V/V)4:1:1). The least polar of the four compounds was identified to be 48b. The most polar spot was identified as the cinchomeronic acid 48a. The compounds with R<sub>f</sub> 0.31 and 0.26 were identified as 3-carbomethoxy-isonicotinic acid 49 and 4-carbomethoxy--nicotinic acid 51, as follows.



Scheme 51

The assignment of structure 51 to the compound with R<sub>f</sub> 0.26 was made by comparing the R<sub>f</sub> of 4-carbomethoxy--

nicotinic acid 51 made by the procedure of Giacomello (Scheme XXVI).<sup>36b</sup> The <sup>1</sup>Hmr spectrum of this compound contained only one ester group and integration showed it to possess the same number of protons as the isomeric ester 3-carbomethoxy-nicotinic acid, 49. The mass spectrum possessed the correct molecular ion at 181 mass units.

Purification of the hydrolysis product was achieved by preparative HPLC using nBuOH:ACOH:H<sub>2</sub>O-4:1:1 as the solvent. The <sup>1</sup>Hmr spectrum of the desired compound 49 in D<sub>2</sub>O exhibited a singlet at 89.25 and doublets at 89.0 and 8.15 integrating to one proton each, which were attributed to the aromatic protons. The methyl group of the ester appeared as a singlet at 84.1. The mass spectrum of the product revealed that it was isomeric with the 51. This hydrolysis procedure was very tedious; it involved evaporating butanol, acetic acid and water, and 3-carbomethoxy-nicotinic acid, 49 also contained 4-carbomethoxy-nicotinic acid, 51 and cinchomeric 48a acid as minor impurities. The material had to be recycled and this process considerably decreased the final yield of the reaction.

#### 5.23 Synthesis of $\beta$ -diazoacetyl nicotinate, 50

The 3-carbomethoxy-nicotinic acid 49 was converted to  $\beta$ -diazoacetyl nicotinate 50 by treating 49 with thionyl chloride followed by reaction with diazomethane. The I.R. spectrum of this compound exhibited a strong band at 2050

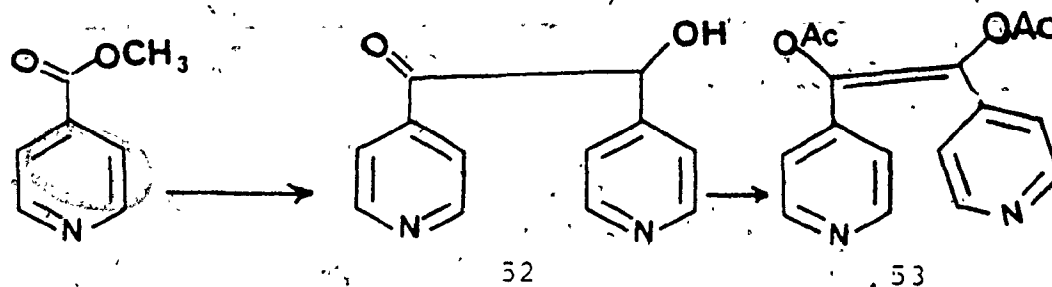
$\text{cm}^{-1}$  indicating the presence of a diazo group. The  $^1\text{Hmr}$  spectrum showed the expected methine ( $\text{CHN}_2$ ) singlet at 85.6.

#### 5.24 Arndt-Eistert rearrangement of 50

With the preparation of  $\beta$ -diazoacetyl nicotinate, 50, the next step of the synthesis, the Arndt-Eistert rearrangement was attempted.  $\beta$ -Diazoacetyl nicotinate 50 was refluxed with silver oxide and methanol and after work-up an 86% yield of  $\gamma$ -homocinchomeric acid dimethyl ester, 38, was obtained.

#### 5.25 Attempted acyloin condensation of methyl isonicotinate

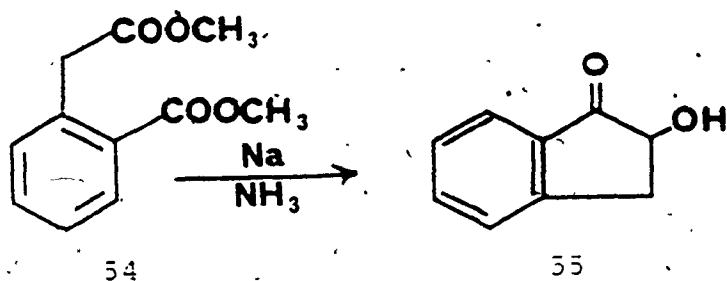
The key step to the synthesis of cyclized heterocyclic hydroxy ketone 37 involves the intramolecular acyloin condensation of  $\gamma$ -homocinchomeric acid dimethyl ester, 38. In order to examine if the acyloin condensation of an ester was possible in the presence of a pyridine nucleus, the intermolecular acyloin condensation of iso-nicotonic ester was examined (Scheme XXVII).



Scheme XXVII



The acyloin condensation of methyl isonicotinate using 1 equivalent of sodium in anhydrous liquid ammonia gave the expected dipyrindoin 52 as a yellow solid. <sup>1</sup>Hmr showed the presence of pyridine nucleus and tlc exhibited the complete absence of the starting methyl isonicotinate. The mass spectrum possessed the correct molecular ion at 214 mass units. The presence of the pyridoin 52 was further confirmed by reaction with acetic anhydride and pyridine to give dipyrindoin diacetate, 53. The mass spectrum possessed the correct molecular ion at 298 mass units.



Scheme XXVIII

#### 5.26. Attempted acyloin condensation of homophthalic dimethyl ester

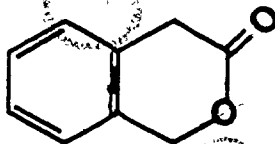
It was also decided to carry out the acyloin condensation of homophthalic dimethyl ester 54, a benzene analogue of  $\gamma$ -homocinchomeric acid dimethyl ester, 38, before an attempt to cyclize the nitrogen analogue (Scheme XXVIII).

### 5.26.1 Synthesis of homophthalic dimethyl ester, 54

Homophthalic acid was converted to homophthalic dimethyl ester 54, with methanol and sulphuric acid, in 92% yield. The  $^1\text{Hmr}$  spectrum of this compound showed the expected two methyl esters as singlets at  $\delta 4.2$  and  $4.1$  respectively. The I.R. spectrum of this compound exhibited a strong band at  $1735\text{ cm}^{-1}$  indicating the presence of the saturated ester group.

### 5.26.2 Attempted cyclization and identification of 56

By analogy with the acyloin condensation of methyl isonicotinate described previously, the homophthalic dimethyl ester 54 would be expected to cyclize to give the desired hydroxy ketone 55. When a solution of homophthalic dimethyl ester, 54 in carefully dried ether was added to a blue coloured solution of sodium in anhydrous ammonia, the blue colour was discharged immediately. After acidic work-up t.l.c. showed the presence of starting material 54 and a new compound, less polar than starting material. Isolation of the new product was performed by preparative tlc.



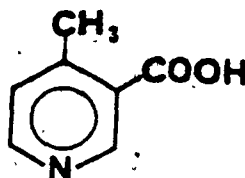
56

The assignment of structure 56 to this new compound was made on the basis of  $^1\text{Hmr}$ , I.R., and mass spectra, and comparison of m.p. with authentic 56. The I.R. spectrum ( $\nu$  1745  $\text{cm}^{-1}$ ) showed the presence of an ester group. The  $^1\text{Hmr}$  spectrum of this compound exhibited two singlets at  $\delta$  5.2 and 3.7 integrating to 2 protons each. The aromatic protons of 56 appeared as a singlet at  $\delta$  7.1. The mass spectrum possessed the correct molecular ion at 148 mass units. The m.p. was found identical with the reported m.p. for 3,6-dihydro-4,5-benzo-2 pyrone 56.<sup>37</sup> Several repetitions of this reaction under carefully dried conditions gave the same product 56.

The failure of homophthalic dimethyl ester, 54, to give hydroxyketone, 37, indicated that the reduction of the aromatic ester group was faster compared to the aliphatic ester in 54 which resulted in the attack of alcohol on the ester functionality to give the cyclized product, 56.

#### 5.27 Attempted acyloin condensation of $\gamma$ -homocinchomeric acid dimethyl ester, 38

By analogy with the acyloin condensation of isonicotinic ester, 38 would be expected to cyclize to give the hydroxyindanone derivative 37. When a solution of 38 in dry ether was added to a blue coloured solution of sodium in liquid ammonia, the blue colour discharged immediately. The compound 57 was isolated in 34% yield, following continuous extraction with ether for 3 days.

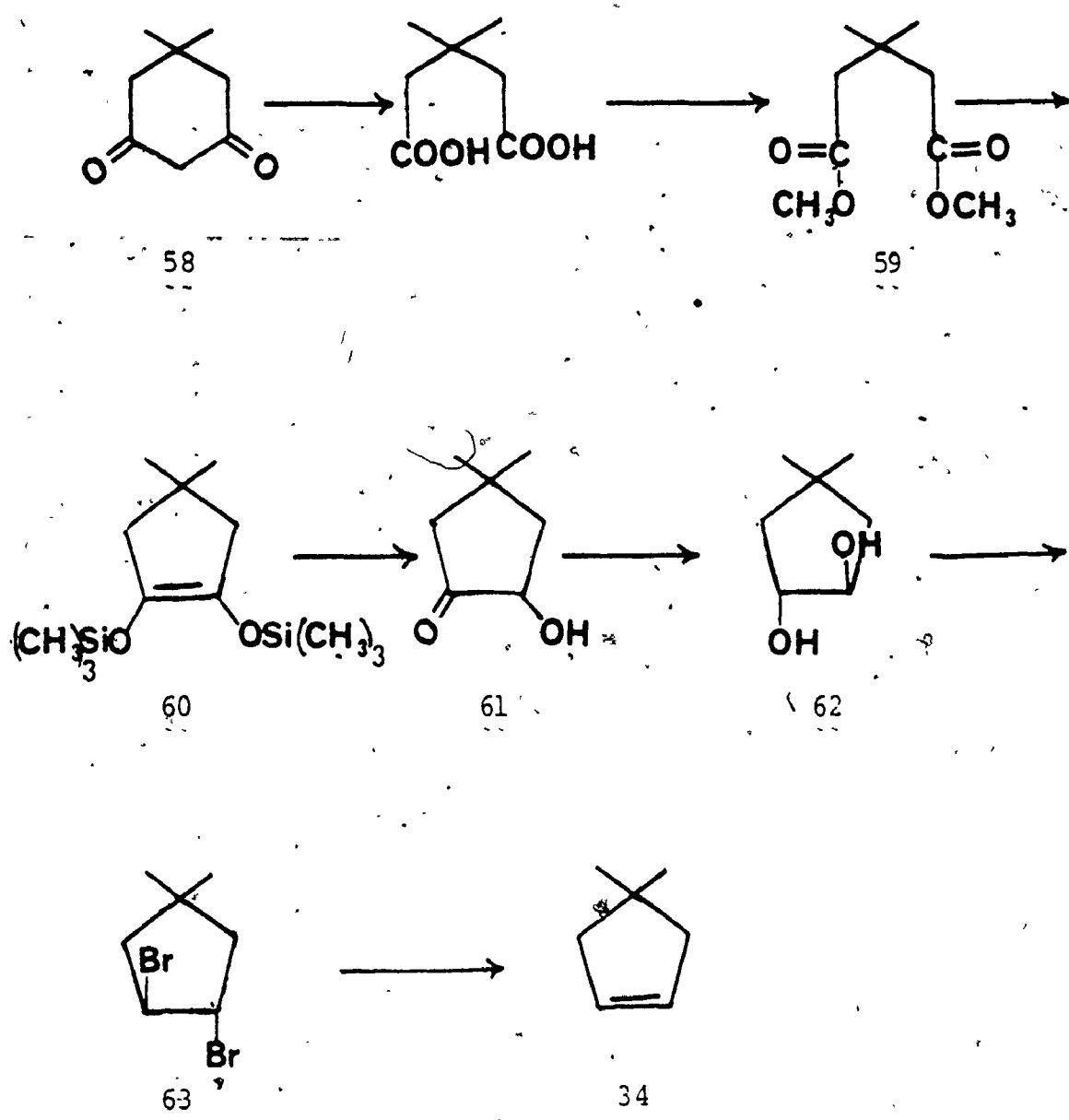


57

The  $^1\text{Hmr}$  spectrum of this compound exhibited a singlet at  $\delta$  2.8 consistent with the new methyl group. The mass spectrum contained the expected molecular ion at 137 a.m.u. The formation of 57 can be considered proceeding via  $\gamma$ -picolinic acid derivative analogous to the example shown in Scheme XXI.

## 2.8 Synthesis of 4,4-dimethylcyclopentene (Scheme XXIX)

The oxidation of dimedone, 58, with sodium oxychloride followed by esterification gave the diester 59 in 84% yield.<sup>39</sup> The  $^1\text{Hmr}$  spectrum of this compound showed the two methyl esters as a singlet at  $\delta$  3.6. Conventional acyloin reaction<sup>37</sup> of the diester 59 results in a very low yield and polymerization; consequently 4,4-dimethyl-1,2-bis-(trimethylsiloxy) cyclopentene, 60, was prepared by performing the acyloin condensation in toluene, followed by



Scheme XXIX

the quenching of the dianions with trimethylsilyl chloride.<sup>40</sup> Hydrolysis of 60 gave the hydroxy-ketone 61.<sup>38</sup> The <sup>1</sup>Hmr spectrum of this compound showed the expected methine multiplet at  $\delta$  4.12. The presence of the hydroxyl group was revealed by a singlet at  $\delta$  3.85 and this proton exchanged readily with D<sub>2</sub>O. Reduction of 61 with lithium aluminium hydride gave the diol 62.<sup>40</sup> The <sup>1</sup>Hmr spectrum of this compound was found identical with that reported in literature. The 1,2-dibromo-4,4-dimethylcyclopentane 63 was synthesized by bromination of 62 with HBr in glacial acetic acid.<sup>38</sup> The <sup>1</sup>Hmr spectrum of this compound, previously unreported, exhibited multiplet at  $\delta$  4.7 integrating to two protons, which was assigned to the methine protons adjacent to bromines. The debromination of 63 has not been attempted yet, owing to the possibility of the resultant product undergoing polymerization in the absence of availability of the reactant 23, the synthesis of which has not been accomplished yet.

## CHAPTER 6

### EXPERIMENTAL

#### 6.1 General

6.1.1 SPECTRA: Infra-red (I.R.) spectra were recorded for Nujol mulls applied to sodium chloride plates or for solutions in sodium chloride cells on a Beckman-Acculab 4 spectrophotometer. Routine <sup>1</sup>Hmr were recorded on a Varian T-60 instrument using tetramethylsilane as the internal standard. For more precise measurements a Varian XL-100 (100 MHz) was used.

6.1.2 MELTING POINTS: Melting points were measured on a Reichert hot stage or a Gallenkamp apparatus and are uncorrected.

6.1.3 CHROMATOGRAPHY: Thinlayer chromatography (tlc) was carried out on Kieselgel GF<sub>254</sub> (Merck). Chromatograms were visualized using medium and low pressure mercury U.V. sources, Iodine vapours or sulphuric acid. Preparative scale TLC (PTLC) was carried out on Kieselgel PF<sub>254</sub>.

6.1.4 AQUEOUS WORK UP: In aqueous work ups the organic layer was washed to neutrality with water, extracted with saturated sodium chloride solution, dried with anhydrous MgSO<sub>4</sub>, and the solvent was evaporated under aspirator vacuum on a rotary evaporator.

### Preparation of $\beta$ -(4-pyridyl)acrylic acid 27

A solution of 2.43 g (0.018 mol) of pyridine 4-carboxaldehyde 26 1.87 g (0.018 mol), malonic acid, and 4 mL of pyridine containing 1 drop of piperidine was refluxed for 4 hr. After cooling the solution, 18 mL of H<sub>2</sub>O was added and the precipitated solid was filtered. The crystals were dried at 70°C giving 3.9 g (93%) of unsaturated acid 27 as a colourless crystalline solid, mp 288°C decomp (lit.<sup>22</sup> 295°C); IR(Nujol)  $\nu_{\max}$  1695, 1600 cm<sup>-1</sup>; <sup>1</sup>Hmr (D<sub>2</sub>O)  $\delta$  8.4 - 8.0 (d, J = 5 Hz, 2H), 7.7 - 7.4 (d, J = 5 Hz, 2H), 7.3 - 7.1 (d, J = 18 Hz, 1H), 6.5 - 6.3 (d, J = 18 Hz, 1H); exact mass calcd. for C<sub>8</sub>H<sub>7</sub>NO<sub>2</sub> 149.0477, found 149.0478.

### Preparation of $\beta$ -(4-pyridyl)propionic acid 29a

The literature procedure<sup>22</sup> for hydrogenation of the double bond in 27 using water as a solvent was very slow therefore the following modified procedure was tried. A mixture of 300 mg of 27, 10 mL CH<sub>3</sub>OH and 10 mg PtO<sub>2</sub> was hydrogenated for 11 hr. Usual work-up gave 298 mg of a white solid, <sup>1</sup>Hmr of which indicated it to contain ~90% unreacted starting material.

About 3.0 g of unsaturated acid was converted into its sodium salt by treating it with aqueous Na<sub>2</sub>CO<sub>3</sub> and this was hydrogenated in the presence of PtO<sub>2</sub> for 26 hr. After filtering the catalyst, the solution was acidified and



up in absolute  $\text{CH}_3\text{OH}$ , filtered and concentrated giving 1.85 g of saturated acid 29a, mp  $223-225^\circ\text{C}$  (lit<sup>22</sup>  $228-230^\circ\text{C}$ );  $^1\text{Hmr}$  ( $\text{D}_2\text{O} + \text{Na}_2\text{CO}_3$ )  $\delta$  8.7 - 8.5 (d,  $J = 5\text{Hz}$ , 2H), 7.6 - 7.2 (d,  $J = 5\text{Hz}$ , 2H), 3.3 - 2.6 (m, 4H); exact mass calcd. for  $\text{C}_8\text{H}_9\text{NO}_2$  151.0633, found 151.0634.

#### Preparation of methyl-( $\beta$ -4-pyridyl)acrylate 28

A solution of 3.0 g (.02 mol) of unsaturated acid 27, 15 mL  $\text{CH}_3\text{OH}$ , and 0.5 mL  $\text{H}_2\text{SO}_4$  was refluxed for 4 hr. After diluting with 50 mL of water, the material was extracted with  $\text{Et}_2\text{O}$  (3 x 100 mL). The organic layer was washed with saturated  $\text{NaHCO}_3$  solution, washed with water, dried and concentrated giving 3.1g (96%) of unsaturated ester 28 as an oil.  $^1\text{Hmr}$  ( $\text{CDCl}_3$ )  $\delta$  8.85 - 8.7 (d,  $J = 5\text{ Hz}$ , 2H), 7.9 - 7.6 (d,  $J = 18\text{Hz}$ , 1H), 7.55 - 7.4 (d,  $J = 5\text{ Hz}$ , 2H), 6.85 - 6.0 (d,  $J = 18\text{Hz}$ , 1H), 4.0 (s, 3H); exact mass calcd. for  $\text{C}_9\text{H}_9\text{NO}_2$  163.0633, found 163.0630.

#### Preparation of methyl-( $\beta$ -4-pyridyl)propionate 29b

A mixture of 1.0 g of methyl-( $\beta$ -4-pyridyl)acrylate, 5.0 mL  $\text{CH}_3\text{OH}$  and 50 mg  $\text{PtO}_2$  was hydrogenated at room temperature and atmospheric pressure for 10 hr. After filtering the catalyst,  $\text{CH}_3\text{OH}$  was evaporated giving a yellow oil which was distilled to give 1.03 g (100%) of saturated ester 29b as a colourless oil, b.p  $70-72^\circ\text{C}/0.5$

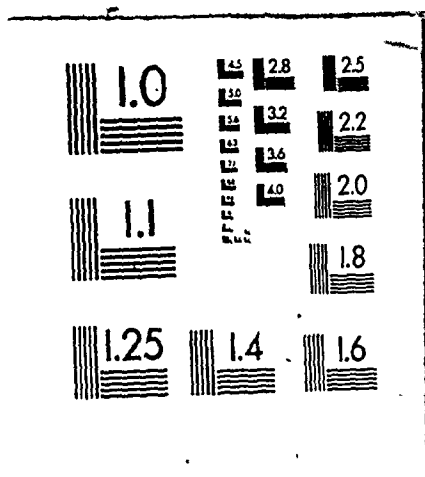
Torr.; I.R. ( $\text{CHCl}_3$ )  $\nu_{\text{max}}$  1745, 1590  $\text{cm}^{-1}$ ;  $^1\text{Hmr}$  ( $\text{CDCl}_3$ )  $\delta$

3.9 (s, 3H), 3.0 - 2.6 (m, 4H); exact mass calcd. for  $C_9H_{11}NO_2$  165.0789, found 165.0786.

**Attempted cyclization of methyl-( $\beta$ -4-pyridyl)propionate, 29b**

A solution of 200mg (1.2 mmol) of 29b in 25 mL dry THF was added with stirring at  $-78^\circ\text{C}$  to a solution of 54 mg (2.4 mg-atom) of sodium in 50 mL anhydrous liquid  $NH_3$  (freshly distilled from Na) and 25 mL dry THF. A few minutes after the addition the blue colour had discharged and the colourless solution was stirred at  $-78^\circ\text{C}$  for 10 minutes more. To this was added 2 mL of  $CH_3OH$  and 10 minutes later saturated  $NH_4Cl$  solution. The ammonia was evaporated over a period of hours and the residue was extracted with  $Et_2O$ . The organic layer was washed with water, dried, and concentrated giving 78 mg of a viscous oil. Basification of the aqueous layer with  $NaHCO_3$  followed by extraction with ether and usual work-up gave 43 mg more (61% total recovery) of the same product. Purification using preparative tlc ( $Et_2O:CH_3OH$  - 60:40) gave 38 mg (31%) of dipyridyl  $\beta$ -ketoester 30 as a colourless oil. I.R. ( $CHCl_3$ )  $\nu_{max}$  1750, 1720  $cm^{-1}$ ;  $^1Hmr$  ( $CDCl_3$ )  $\delta$  8.5 - 8.3 (d,  $J$  = 5 Hz, 4H), 7.2 - 7.0 (d,  $J$  = 5 Hz, 4H), 4.2 - 4.0 (t,  $J$  = 8 Hz, 1H), 4.1 (s, 3H), 3.6 - 3.3 (d,  $J$  = 8 Hz, 2H), 3.2 - 3.0 (m, 4H); mass spectrum  $m/e$  (rel. intensity) 298 (32%), 240 (13%), 106 (100%). The less polar band from the preparative plate gave 12 mg of unreacted 29b.

3 3  
OF / DE



### Preparation of dipyridyl $\beta$ -ketoester 30

A solution of 278 mg (1.68 mmol) of 29b, 10 mL xylene and 54 mg (0.084 mmol)  $\text{CH}_3\text{ONa}$  was refluxed for 10 hr. After cooling, the solution was diluted with 10 mL of water and extracted with ether. The organic layer was dried and concentrated giving 220 mg of an oil. Preparative tlc gave 98 mg (47%) of  $\beta$ -keto ester 30 and 44 mg of unreacted ester.

### Preparation of N-Benzylpyridinium methyl propionate 3la

A solution of 100 mg (0.6 mmol) of methyl pyridyl-propionate 29b, 124 mg (0.72 mmol) of benzylbromide in 5.0 mL dry EtOAc was refluxed for 1 hr. After cooling, the solid was filtered and washed with cold EtOAc giving 120 mg (80%) of colourless crystals of pyridinium salt 3la which appeared to be hygroscopic. I.R. ( $\text{CHCl}_3$ )  $\nu_{\text{max}}$   $1730\text{ cm}^{-1}$ ;  $^1\text{Hmr}$  ( $\text{CDCl}_3$ )  $\delta$  9.6 - 9.4 (d,  $J = 5\text{ Hz}$ , 2H), 8.3 - 8.1 (d,  $J = 5\text{ Hz}$ , 2H), 8.0 - 7.4 (m, 5H), 6.5 (s, 2H), 4.0 (s, 3H), 3.6 - 3.3 (d,  $J = 8\text{ Hz}$ , 2H), 3.25 - 3.0 (d,  $J = 8\text{ Hz}$ , 2H); mass spectrum (70 eV)  $m/e$  (rel. intensity) 255 (33%), 196 (100%), 165 (53%).

### Preparation of N-triphenylmethyl pyridinium methyl propionate 3lb

To a stirred solution of 200 mg (1.21 mmol) of methyl pyridyl propionate 29b in 5 mL of dry  $\text{CH}_2\text{Cl}_2$  (distilled from  $\text{CaH}_2$ ) at room temperature, was added a solution of 163 mg (0.51 mmol) of triphenylmethylfluoroborate in 4.0 mL of

dry  $\text{CH}_2\text{Cl}_2$ . Immediately after mixing the reagents the yellow colour of the solution had discharged and a solid had precipitated. The yellow solid was filtered and washed with hexane under nitrogen to give 486 mg of pyridinium salt 31b as a cream yellow solid which appeared to be hygroscopic.  $^1\text{Hmr}$  ( $\text{CDCl}_3$ ) 9.1 - 8.9 (d,  $J = 6\text{Hz}$ , 2H), 8.3 - 8.0 (d,  $J = 6\text{Hz}$ , 2H), 7.4 (s, 15H), 4.05 (s, 3H), 3.6 - 3.4 (d,  $J = 8\text{Hz}$ , 2H), 3.3 - 3.1 (d,  $J = 8\text{Hz}$ , 2H).

Reduction and attempted cyclization of N-benzylpyridinium methyl propionate 31a.

Reduction of 31a was carried out using the procedure of Buchi.<sup>26</sup> To a vigorously stirred solution of 88 mg (0.37 mmol) of 31a in 1.0 mL  $\text{H}_2\text{O}$  at  $0^\circ\text{C}$  was added a saturated aqueous  $\text{Na}_2\text{CO}_3$  (80 mg  $\text{Na}_2\text{CO}_3$ /1.0 mL  $\text{H}_2\text{O}$ ) followed by dropwise addition of a solution of  $\text{NaBH}_4$  (16 mg, 0.42 mmol) in 3 mL dilute  $\text{Na}_2\text{CO}_3$  solution. The resulting mixture was taken up in 25 mL  $\text{CHCl}_3$ , washed with water, dried and concentrated giving 49 mg dihydropyridine ester 32 as an oil.  $^1\text{Hmr}$  ( $\text{CDCl}_3$ )  $\delta$  7.2 (s, 5H), 6.2 - 6.0 (d,  $J = 8\text{Hz}$ , 1H), 4.8 - 4.6 (m, 1H), 4.1 (m, 1H), 4.1 - 3.8 (s, overlapped by multiplet, 5H), 3.0 - 2.6 (d,  $J = 8\text{Hz}$ , 4H).

The cyclization of the dihydropyridine ester 32 was carried out using the procedure of Meyers.<sup>24</sup> A solution of 63 mg of dihydropyridine ester prepared above, in 10 mL of toluene containing 2 drops of  $\text{CF}_3\text{COOH}$  was refluxed using a Dean-Stark apparatus for 30 hr. After cooling to room

temperature, the solution was successively washed with  $\text{NaHCO}_3$  and  $\text{H}_2\text{O}$ . The organic layer was dried and concentrated giving 56 mg of an oil, tlc of which failed to show a positive DNP test.

#### Preparation of 4-Pyridyl-acetaldehyde diethylacetal, 36

To a stirred solution of 2.0 g (0.21 mmol) of  $\gamma$ -picoline 35 in 10 mL of dry THF at  $-20^\circ\text{C}$  under  $\text{N}_2$  was added 8.6 mL (0.21 mmol) of  $n\text{-BuLi}$  in hexane. The cooling bath was removed and the mixture was allowed to reach ambient temperature. To this was added with stirring a solution of 4.23 g (0.21 mmol) of bromoacetaldehyde diethyl acetal in 10 mL of dry THF over a period of 5 minutes. After stirring the viscous red slurry for 1 hr, 20 mL of  $\text{H}_2\text{O}$  was added and it was extracted with ether (3x50 mL). The organic layer was washed with water, dried and concentrated giving 4.5 g of viscous yellow oil. Kugelrohr distillation ( $116 - 124^\circ\text{C}/8\text{Torr}$ ) gave 3.98 g (88%) of 36 as an oil.  $^1\text{HMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.43 - 8.3 (d,  $J = 5\text{Hz}$ , 2H), 7.4-7.2 (d,  $J = 5\text{Hz}$ , 2H), 3.8-3.2 (m, 4H), 3.0 - 2.4 (m, 2H), 2.0 - 1.6 (m, 2H), 1.4 - 1.0 (t,  $J = 8\text{Hz}$ , 6H); Exact mass calcd. for  $\text{C}_{12}\text{H}_{19}\text{NO}_2$  209.1415, found 209.1419.

#### Preparation of 4-Pyridyl propionaldehyde 34

A mixture of 340 mg of 36 and 4 mL of aqueous 10%  $\text{HCl}$  was stirred for 5 hr. After neutralizing the acid with  $\text{NaHCO}_3$ , the material was extracted with  $\text{CH}_2\text{Cl}_2$  (5x20 mL).

The organic layer was dried and concentrated giving 63 mg (47%) of aldehyde 34 as an oil, b.p. 148°C/4 Torr; IR (CHCl<sub>3</sub>)  $\nu_{\text{max}}$  1715, 1590 cm<sup>-1</sup>; <sup>1</sup>Hmr (CDCl<sub>3</sub>)  $\delta$  9.5 - 9.4 (s, 1H), 8.4 - 8.2 (d, J = 5Hz, 2H), 7.3 - 7.0 (d, J = 5Hz, 2H), 3.0 - 2.8 (m, 4H); mass spectrum (70 eV) m/e (relative intensity) 135 (10%), 104 (15%), 83 (100%).

Attempted cyclization of 4-Pyridyl propionaldehyde 34 to 5,6-dihydro-2-pyridin-7-one 25

Procedure 1: The procedure of Carona<sup>27</sup> for homolytic acylation of protonated pyridines was used. To an ice cold stirred solution of 235 mg (1.74 mmol) of 34, 2.6 mL of H<sub>2</sub>O, 2.6 mL glacial HOAc, and 0.52 mL conc. H<sub>2</sub>SO<sub>4</sub> was added 0.3 mL (3.58 mmol) of *t*-butylhydroperoxide followed by a solution of 0.96 g (3.58 mmol) of FeSO<sub>4</sub> in 5.0 mL H<sub>2</sub>O, and the solution was stirred at ice temperature for 2 hr. After neutralizing the acid with NaHCO<sub>3</sub>, the reaction mixture was extracted with ether. The organic layer was dried and concentrated giving an oil. TLC and the spectra indicated this to be unreacted aldehyde 34 only, with no cyclization product.

Procedure 2: A mixture of 63 mg (0.46 mmol) of 34 and 6 mg (0.046 mmol) of di-*t*-butylperoxide was heated at 100°C for 5 hr. The <sup>1</sup>Hmr spectrum of the crude product showed 60% loss of the aldehyde function and absence of the cyclization product. Prolonged heating of the mixture of aldehyde and peroxide resulted in polymerization.

### Methyl nicotinate

Dry HCl(g) was bubbled into a refluxing solution of 15 g of nicotinic acid and 100 mL CH<sub>3</sub>OH for 5 h. After distilling the CH<sub>3</sub>OH, the mixture was neutralized using aq. NaHCO<sub>3</sub>. The residue was extracted with Et<sub>2</sub>O (3x100 mL), and the organic layer was washed with water, dried, and concentrated giving 14.6 g (87.4%) of methyl nicotinate as a colourless liquid. <sup>1</sup>Hmr (CDCl<sub>3</sub>) δ 9.0 (d, J = 2Hz, 1H), 8.8 - 8.6 (dd, J = 5Hz, 2Hz, 1H) 8.3 - 8.0 (dd, J = 8Hz, 2Hz, 1H), 7.5 - 7.2 (dd, J = 8Hz, 5Hz, 1H), 4.0 (s, 3H).

### 2-(3-Pyridyl)-4,4-dimethyl-Δ<sup>2</sup>-oxazoline 39a

Procedure 1: A solution of 5.0 g (0.036 mol) of methyl nicotinate and 3.88 g of 2-amino-2-methyl-1-propanol was refluxed for 3 h under N<sub>2</sub>. At the end of the reaction excess aminoalcohol was distilled (110°C/0.1 Torr) giving the solid amide, 39', IR (CHCl<sub>3</sub>) ν<sub>max</sub> 3550-3400, 1680 cm<sup>-1</sup>; <sup>1</sup>Hmr (CDCl<sub>3</sub>) δ 8.9 - 8.8 (d, J = 5Hz, 1H), 8.6 - 8.4 (dd, J = 5Hz, 2Hz, 1H), 8.0 - 7.8 (dd, J = 8Hz, 2Hz, 1H), 7.5 - 7.2 (dd, J = 8Hz, 5Hz, 1H), 6.8 - 6.6 (brs, 1H exchanged with D<sub>2</sub>O), 4.7 (s, 1H), 3.8 (s, 2H), 1.6 (s, 6H).

To the above amide was added 50 mL SOCl<sub>2</sub> and the mixture was stirred at room temperature for 3 hr at which point all solids had gone into solution. After distilling unreacted SOCl<sub>2</sub>, the residue was treated with 20% methanolic-KOH for 3 hr. Methanol was distilled and the residue was taken up in Et<sub>2</sub>O and washed with water. The



organic layer was dried and concentrated giving 3.9 g (60%) of 2-(3-pyridyl)4,4-dimethyl- $\Delta^2$ -oxazoline, 39a as a colourless liquid. IR(CHCl<sub>3</sub>) 1640, 1580, 1295 cm<sup>-1</sup>; <sup>1</sup>Hmr (CDCl<sub>3</sub>)  $\delta$  9.0 (s, 1H), 8.6-8.4 (d, J = 5.0, 2.0 Hz, 1H), 8.1 (dd, J = 5 Hz, 2.0 Hz, 1H), 7.2 (dd, J = 8.0 Hz, 5.0 Hz, 1H), 4.0 (s, 2H), 1.33 (s, 6H); exact mass calcd. for C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O 176.0959, found 176.0959.

Procedure 2: A mixture of 120 g (0.16 mol) of nicotinic acid and 60 mL of SOCl<sub>2</sub> was stirred at room temperature overnight. Distillation of unreacted SOCl<sub>2</sub> gave nicotinic acid chloride hydrochloride as a colourless solid. This was added slowly to a stirred solution of 43.7 g (0.48 mol) of 2-amino-2-methyl-1-propanol in 400 mL CH<sub>2</sub>Cl<sub>2</sub> at 0°C. The temperature was raised to 25°C and the mixture was stirred at this temperature for 48 hr. Precipitated amine hydrochloride was filtered off and washed thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The filtrate was concentrated giving the amide contaminated with 2-amino-2-methyl-1-propanol the latter was removed under vacuum (110/0.1 Torr).

The above amide was stirred at room temperature with 50 mL SOCl<sub>2</sub> for 30 minutes, at the end of which all solids had gone into solution. This was added to an ice-cold solution of excess 20% aqueous NaOH. A vigorous reaction ensued, which soon subsided. The material was extracted with ether, the organic layer was washed with water, dried, and concentrated giving 15 g (52.4%) of oxazoline derivative

spectra were as outlined above.

#### Attempted preparation of 4-ethylacetate-pyridyl- $\Delta^2$ -oxazoline 40

A solution of 180 mg (1.0 mmol) of 2-(3-Pyridyl)-4,4-dimethyl- $\Delta^2$ -oxazoline 39a in 10 mL dry THF was added at 0°C to a stirred solution of lithium 2,2,6,6-tetramethyl piperidide (1.1 mmol, prepared using 2,2,6,6-tetramethyl-piperidine and *n*-BuLi/hexane in 6.0 mL dry THF at 0°C). The resulting solution was stirred at the same temperature for 1 hr. To this was added 0.128 mL (1.1 mmol) of ethyl bromoacetate and the solution was allowed to warm to 25°C and stirred for 5 hr. Saturated  $\text{NH}_4\text{Cl}$  solution was then added and the mixture was extracted with ether. The organic layer was washed with water, dried, and concentrated giving a viscous oil. This material was purified using preparative tlc ( $\text{Et}_2\text{O}$ , two developments) giving 61 mg (27%) of the 4-bromo-pyridyl- $\Delta^2$ -oxazoline derivative 41 as a yellow coloured liquid.  $^1\text{Hmr}$  ( $\text{CDCl}_3$ )  $\delta$  8.8 (s, 1H), 8.3 (d,  $J = 5\text{Hz}$ , 1H), 7.12 (d,  $J = 5\text{Hz}$ , 1H), 4.1 (s, 2H), 1.2 (s, 6H); exact mass calcd. for  $\text{C}_{10}\text{H}_{11}\text{N}_2\text{OBr}$  254.0052, found 254.0055; mass spectrum (70 eV)  $m/e$  (rel. intensity) 256 (95%), 254 (100%).

#### Preparation of 2-(3-Pyridyl)-4,4-dimethyl- $\Delta^2$ -oxazoline nitro derivative 42

Lithium 2,2,6,6-tetramethyl piperidide (1.3 mmol) was

prepared by mixing 2,2,6,6-tetramethylpiperidine and  $n$ -BuLi/hexane in dry THF at 0°C. To this was added a solution of 2-(3-Pyridyl)4,4-dimethyl- $\Delta^2$ -oxazoline 39a (1.19 mmol) in 8 mL dry THF and the solution was stirred at 0°C for 1 hr. After adding a solution of nitroethylene [2 M, prepared by phthalic anhydride dehydration of 2-nitroethanol]<sup>32</sup> in dry C<sub>6</sub>H<sub>6</sub>, the solution was warmed to 25°C and stirred for 5 hr. The reaction mixture was poured into saturated NH<sub>4</sub>Cl and extracted with Et<sub>2</sub>O. The organic layer was washed with water, dried, and concentrated giving 239 mg of a colourless oil. Purification was done using preparative tlc (Et<sub>2</sub>O as a solvent) giving three compounds: 1) Colourless oil (28 mg) of unknown structure, IR (CHCl<sub>3</sub>)  $\nu_{\max}$  1650, 1600, 1560 cm<sup>-1</sup>; <sup>1</sup>Hmr (CDCl<sub>3</sub>)  $\delta$  9.0 (s, 1H), 8.6 (d, J = 5Hz, 1H), 7.3 (d, J = 5Hz, 1H), 4.8 - 4.2 (m, 3-4 H), 4.0 (m, 2H), 1.33 (s, 6H). 2) 2-(3-Pyridyl)4,4-dimethyl- $\Delta^2$ -oxazoline nitro derivative 42 (23 mg, 10%) colourless liquid. IR(CHCl<sub>3</sub>)  $\nu_{\max}$  1650, 1600, 1560 cm<sup>-1</sup>; <sup>1</sup>Hmr (CDCl<sub>3</sub>)  $\delta$  8.9 (brs, 2H), 7.2 (d, 1H), 5.8 - 4.6 (t, J = 8Hz, 2H), 4.02 (s, 2H), 3.7 - 3.4 (t, J = 8Hz, 2H), 1.3 (s, 6H). 3) unreacted starting 3-pyridyl- $\Delta^2$ -oxazoline 39a.

Attempted preparation of 1,4-dihydropyridine 4- $t$ -butyl ester- $\Delta^2$ -oxazoline (43a).

To a stirred solution of lithium isopropylcyclo-

hexylamine (1.24 mmol) [prepared using isopropylcyclohexylamine,  $n$ -BuLi hexane in 5 mL dry THF at  $-78^{\circ}\text{C}$  under  $\text{N}_2$  atmosphere] was added a solution of  $t$ -butylacetate (1.2 mmol) in 5.0 mL dry THF and the temperature was raised slowly from  $-78^{\circ}\text{C}$  to  $0^{\circ}\text{C}$ . To this was added a solution of 2-(3-pyridyl)-4,4 dimethyl- $\Delta^2$ -oxazoline 39a (1.13 mmol) in 5.0 mL dry THF, the temperature was raised to  $25^{\circ}\text{C}$  and the solution was stirred at this temperature for 5 h. Usual work-up gave 349 mg of pale yellow oil. Distillation under reduced pressure gave 176 mg of starting oxazoline derivative 39a.

**Attempted preparation of 1,4-dihydropyridine-3-oxazoline derivative (43b)**

Lithium diisopropylamide was made by adding  $n$ -BuLi/hexane (1.13 mmol) to an ice cold stirred solution of diisopropylamine (1.26 mmol) in 4 mL dry THF under  $\text{N}_2$ . This was stirred for  $\frac{1}{2}$  h more and to it was added at  $0-5^{\circ}\text{C}$  3 mL dry THF containing dry HOAc (1.26 mmol). The reaction mixture was stirred at the same temperature for 3.5 h and to it was then added oxazoline derivative 39a (1.03 mmol) in 4.0 mL dry THF. The reaction mixture was stirred at  $5^{\circ}\text{C}$  for 2 hr and then at room temperature for 5 h. After adding  $\text{H}_2\text{O}$ , THF was evaporated and the solution was acidified with dilute HCl to pH 3. Extraction with  $\text{Et}_2\text{O}$ , washing with water, drying and concentration gave 143 mg of a colourless oil. The material was purified using

preparative tlc (EtOAc:CH<sub>3</sub>OH-90:10) giving 125 mg of unreacted 3-pyridyl- $\Delta^2$ -oxazoline derivative 39a. From the band at R<sub>f</sub> 0.36 was obtained 37 mg of reddish liquid.

Rechromatography of this (EtOAc:CH<sub>3</sub>OH-70:30) gave 13 mg (6%) of 44b as a yellowish liquid. <sup>1</sup>Hmr (CDCl<sub>3</sub>)  $\delta$  9.1 (s, 1H), 8.2 - 8 (dd, J = 8 Hz, 2Hz, 1H), 7.4 - 7.2 (dd, J = 8Hz, 2Hz, 1H), 4.1 (s, 2H), 2.5 (s, 3H), 1.2 (s, 6H); IR (CHCl<sub>3</sub>) 1645, 1580 cm<sup>-1</sup>; mass spectrum (70 eV) m/e (rel. intensity) 190 (18%), 176 (36%), 175 (100%) 160 (39%).

Also isolated from the above plate was 7 mg of the dimer of 2-(3-pyridyl)-4,4-dimethyl- $\Delta^2$ -oxazoline, 45. <sup>1</sup>Hmr (CDCl<sub>3</sub>)  $\delta$  9.2 - 9.0 (m, 2H), 8.9 - 8.7 (m, 1H), 8.3 - 8.1 (m, 1H), 7.7 - 7.5 (m, 2H), 4.3 (s, 2H), 4.1 (s, 2H), 1.2 (2 overlapping s, 12H). Impurity at  $\delta$  2.1, 1.0; mass spectrum (70 eV) m/e (rel. intensity) 350 (47%), 335 (24.6%), 275 (20.2%), 231 (100%).

#### Preparation of 1,4 dihydropyridine-3-oxazoline derivative 43c

To a stirred solution of 300 mg (1.7 mmol) of 3-pyridyl- $\Delta^2$ -oxazoline 39a in 9.0 mL dry THF at -78°C was added 2.204 mmol of lithioacetonitrile (by treating acetonitrile with lithium diisopropylamide in THF at -78°C) and the yellow solution was stirred at -78°C for 1 h. After allowing the solution to warm to 0°C over 1 hr, the reaction mixture was poured into saturated NH<sub>4</sub>Cl solution and extracted with ether. The organic layer was washed

191  
with water, dried and concentrated giving 239 mg (65%) of the dihydropyridine derivative as a colourless liquid. The reported yield was 32%.<sup>28a</sup> mp 124-126°C (lit.<sup>28a</sup>, 124-125°C); <sup>1</sup>Hmr (CDCl<sub>3</sub>) 7.06 (dd, J = 5Hz, 2Hz, 1H), 6.7 - 6.3 (m, 2H), 4.76 (m, 1H), 3.9 (s, 2H), 3.7 - 2.1 (m, 3H), 1.3 (s, 3H), 1.25 (s, 3H).

**Preparation of 2(3-pyridyl)-4,4-dimethyl- $\Delta^2$ -oxazoline derivative 46.**

A solution of 757 mg (3.47 mmol) of dihydropyridine derivative 43c, 790 mg chloranil (3.1 mmol) and 100 mL toluene was refluxed for 3 h. After cooling, the solution was extracted with 12% NaOH till colourless. The organic layer was washed with water, dried, and concentrated giving 645 mg (81%) of pyridine 3-oxazoline derivative 46 as a colourless solid, mp 90-92°C (lit.<sup>28a</sup> 90-91°C); IR(CHCl<sub>3</sub>)  $\nu_{\text{max}}$  1650, 1600 cm<sup>-1</sup>; <sup>1</sup>Hmr (CDCl<sub>3</sub>) 9.0 (s, 1H), 8.6 (d, J = 5Hz, 1H), 7.5 (d, J = 5Hz, 1H), 4.3 (s, 2H), 4.0 (s, 2H), 1.28 (s, 6H); exact mass calcd. for C<sub>12</sub>H<sub>13</sub>N<sub>3</sub>O 176.0960, found 176.0959.

**Attempted acid hydrolysis of 2(3-pyridyl)-4,4-dimethyl- $\Delta^2$ -oxazoline derivatives 46**

Procedure 1: A solution of 10 mg of 46 and 4 mL of absolute EtOH saturated with HCl (g) was allowed to stand at room temperature for 20 h. After basification to pH 8, the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5x10 mL). The

organic layer was washed with water, dried and concentrated giving 7 mg of unsaturated lactam 47c as a colourless semi-solid, IR(CHCl<sub>3</sub>)  $\nu_{\max}$  1635, 1680 cm<sup>-1</sup>; <sup>1</sup>Hmr (CDCl<sub>3</sub>) 8.8 - 8.7 (brs, 1H), 8.3 - 8.14 (d, J = 5Hz, 1H), 7.1 - 6.9 (d, J = 5Hz, 1H), 5.6 (s, 1H), 4.2 (s, 2H), 1.35 (s, 6H); exact mass calcd. for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> 216.0900, found 216.0900.

Procedure 2: A mixture of 9.0 mg of 46 and 1.0 mL conc. HCl was refluxed for 18 h. Work-up as above gave 7 mg unsaturated lactam 47c as a colourless semi-solid. Physical constants and spectra were as outlined above.

#### Preparation of $\gamma$ -Homocinchomeric acid dimethylester 38

A solution of 30 mg of 46 and 20 mL of 10% ethanolic KOH was refluxed for 8 h at the end of which tlc indicated complete absence of starting material. After neutralizing the solution with acid (HCl), it was concentrated to dryness and to the residue was added an ethereal solution of CH<sub>2</sub>N<sub>2</sub>. After ½ h excess CH<sub>2</sub>N<sub>2</sub> was decomposed using HOAc and the solution was concentrated, taken up in ether, washed with water, dried, and concentrated giving 20 mg of an oil. The material was purified using preparative tlc (10x20 cm SiO<sub>2</sub> plate, developed twice using Et<sub>2</sub>O) giving 3 mg (10%) of  $\gamma$ -homocinchomeric acid dimethylester, IR(CHCl<sub>3</sub>)  $\nu_{\max}$  1725, 1595 cm<sup>-1</sup>; exact mass calcd. for C<sub>10</sub>H<sub>11</sub>NO<sub>4</sub> 209.0688, found 209.0688 and 5 mg of 47c, physical constants and spectra were as outlined above.

**Attempted basic hydrolysis of 2(3-pyridyl)-4,4 dimethyl- $\Delta^2$ -oxazoline derivative 46**

A solution of 15 mg of 46 in 2.0 mL DMSO containing 0.7 mL of 5% aqueous NaOH was allowed to stand at room temperature. At the end of 2 h tlc (Et<sub>2</sub>O, three developments) indicated complete absence of starting material and presence of the unsaturated lactam 47c only.

**Improved preparation of  $\gamma$ -Homocinchomeric acid dimethyl ester 38**

A solution of 1.69 g of 46 and 30 mL of 10% KOH in C<sub>2</sub>H<sub>5</sub>OH:H<sub>2</sub>O (v 1/1) was refluxed for 31 hrs. After evaporating the solution to dryness excess ethereal diazomethane was added and solution was stirred at room temperature for  $\frac{1}{2}$  h. Unreacted CH<sub>2</sub>N<sub>2</sub> was destroyed using HOAc and the ether layer was dried, and concentrated giving 1.56 g of an oil. Purification using flash column chromatography gave 628 mg (39%) of  $\gamma$ -homocinchomeric acid dimethyl ester 38 as a colourless oil. IR(CHCl<sub>3</sub>) 1725, 1600 cm<sup>-1</sup>; <sup>1</sup>Hmr (CDCl<sub>3</sub>)  $\delta$  8.9 (s, 1H), 8.5 (d, J = 5Hz, 1H), 7.0 (d, J = 5Hz, 1H), 4.0 (s, 2H), 3.8 (s, 3H), 3.6 (s, 3H); exact mass calcd. for C<sub>10</sub>H<sub>11</sub>NO<sub>4</sub> 209.0688, found 209.0688.

**Cinchomeric acid dimethyl ester 48b<sup>36</sup>**

A solution of 14 g of cinchomeric acid 48a in 150 mL CH<sub>3</sub>OH was refluxed and through it was bubbled dry HCl (g)



was neutralized with  $\text{NaHCO}_3$  solution. Extraction of the material with ether, washing with water, drying and concentration gave 10.4 g of 48b as a colourless liquid.

IR( $\text{CHCl}_3$ ) 1730, 1600  $\text{cm}^{-1}$ ;  $^1\text{Hmr}$  ( $\text{CDCl}_3$ )  $\delta$  8.5 (s, 1H), 8.35 - 8.2 (d,  $J = 5\text{Hz}$ , 1H), 7.4 - 7.3 (d,  $J = 5\text{Hz}$ , 1H), 3.8 (s, 6H).

#### 4-Carbomethoxy-nicotinic acid 51

This compound was synthesized using the procedure of Giacomello<sup>36</sup> by refluxing a solution of 500 mg cinchomeric anhydride in 5 mL dry  $\text{CH}_3\text{OH}$ . mp 151-152°C (lit<sup>36</sup> 153-154°C);  $^1\text{Hmr}$  ( $\text{D}_2\text{O}$ )  $\delta$  8.8 - 8.5 (m, 2H), 7.8 - 7.6 (d,  $J = 5\text{Hz}$ , 1H), 3.8 (s, 3H); exact mass calcd. for  $\text{C}_8\text{H}_7\text{NO}_4$ : 181.0375, found 181.0373.

#### 3-Carbomethoxy-nicotinic acid 49

A solution of 3.58 g (0.18 mmol) cinchomeric dimethyl ester 48b and 34.7 mL of 0.53 N methanolic KOH was kept at -10°C for 2 days. After distilling the  $\text{CH}_3\text{OH}$ , 5 mL of water was added and the material was extracted with ether (30 mL). The organic layer was dried and concentrated giving 502 mg (14%) of 48a as a colourless liquid.

The aqueous layer from above was acidified to pH = 4 and water was evaporated under reduced pressure giving 3.29 g of solid. Tlc ( $n\text{-BuOH}:\text{HOAc}:\text{H}_2\text{O}-4:1:1$ ) showed this to contain 48b ( $R_f$  0.50), 49 ( $R_f$  0.31), 51 ( $R_f$  0.26), and 48a ( $R_f$  0.15). Purification using preparative HPLC (Water

Associates Prep LC 500A, prepak-500/silica column and RI detector) using  $n$ -BuOH:HOAc:H<sub>2</sub>O - 4:1:1 gave 540 mg of 49 (R<sub>f</sub> 0.31) contaminated with 51 and 48a. Further purification was carried out by recycling the above material through the preparative HPLC giving 310 mg of 49 as a colourless crystalline solid. Recrystallized from CH<sub>3</sub>OH. mp 170-176°C (lit.<sup>36a</sup> 182°C); <sup>1</sup>Hmr (D<sub>2</sub>O)  $\delta$  9.3 - 9.2 (s, 1H), 9.15 - 9.0 (d, J = 5Hz, 1H), 8.2 - 8.1 (d, J = 5Hz, 1H), 4.1 (s, 3H); exact mass calcd. for C<sub>8</sub>H<sub>7</sub>NO<sub>4</sub>: 181.0375, found: 181.0372.

#### Methyl $\beta$ -diazoacetyl nicotinate 50

A solution of 193 mg of 49 and 4 mL of SOCl<sub>2</sub> [distilled from (C<sub>2</sub>H<sub>5</sub>O)<sub>3</sub>P] was refluxed for 3 h. After evaporating SOCl<sub>2</sub>, the residue was distilled giving 169 mg of nicotine ester acid chloride, b.p. 130 - 135°C 0.1 Torr. A solution of the above nicotinic ester acid chloride and excess CH<sub>2</sub>N<sub>2</sub> in Et<sub>2</sub>O was allowed to stand at room temperature for 10 min.; the liquid portion was evaporated in a stream of N<sub>2</sub>, the residue was taken in Et<sub>2</sub>O, filtered and concentrated giving 143 mg of crude diazonicotinate 50. Purification by flash column chromatography (Et<sub>2</sub>O as solvent) gave 98 mg (45%) of pure methyl  $\beta$ -diazoacetyl nicotinate 50 as a liquid. IR(CHCl<sub>3</sub>)  $\nu_{\max}$  2050, 1730, 1615 cm<sup>-1</sup>; <sup>1</sup>Hmr (CDCl<sub>3</sub>) 8.9 - 8.4 (brs, 2H), 7.4 - 7.2 (d, J = 5Hz, 1H), 5.6 (s, 1H), 3.9 (s, 3H).

**$\gamma$ -Homocinchomeric acid dimethyl ester 38**

A mixture of 74 mg of methyl  $\beta$ -diazoacetyl nicotinate 50, 10 mg  $\text{Ag}_2\text{O}$  and 10 mL dry  $\text{CH}_3\text{OH}$  was refluxed for 2 h. After cooling, the mixture was filtered through celite and concentrated giving 69 mg (86%) of 38. Physical constants and spectra were as outlined previously.

**Acyloln condensation of methyl isonicotinate to dipyridoin 52**

A solution of 1.0 g (0.01 mol) of ester in 20 mL dry  $\text{Et}_2\text{O}$  was added slowly to a stirred solution containing 335 mg (0.015 g atom) of Na, 30 mL of anhydrous liquid  $\text{NH}_3$  (freshly distilled from Na), and 20 mL dry  $\text{Et}_2\text{O}$  at  $-78^\circ\text{C}$  under  $\text{N}_2$ . After stirring the mixture at  $-78^\circ\text{C}$  for 3 hr, 20 mL  $\text{Et}_2\text{O}$  containing 10 mL  $\text{CH}_3\text{OH}$  was added (solution yellow) and stirred for 10 minutes at the same temperature. The reaction mixture was quenched using saturated  $\text{NH}_4\text{Cl}$  and  $\text{NH}_3$  was evaporated over a period of hours. The residual mixture was subjected to continuous  $\text{Et}_2\text{O}$  extraction for 2 days. The ether layer was dried and concentrated giving 0.630 g of dipyridoin as a yellow crystalline solid, mp  $210 - 214^\circ\text{C}$ ;  $^1\text{Hmr}$  ( $\text{CDCl}_3$ ) 8.4 - 8.0 (m, 4H), 7.8 - 7.0 (m, 4H); exact mass calcd. for  $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_2$  214.0742, found 214.0741.

The diol was acetylated using the standard procedure ( $\text{Ac}_2\text{O}$  + pyridine) and purified by preparative tlc (Hexane: $\text{EtOAc}$  - 50:50) giving pyridoin diacetate 53 as a yellow solid.

### Preparation of homophthalic acid dimethyl ester 54

A solution of 2.0 g of homophthalic acid in 15 mL  $\text{CH}_3\text{OH}$  was refluxed for 4 h. The reaction mixture was diluted with water and extracted with  $\text{Et}_2\text{O}$  (3x100 mL). The organic layer was washed with  $\text{H}_2\text{O}$ , dried, and concentrated giving 2.14 g (92.8%) of homophthalic acid dimethyl ester as a colourless liquid. IR( $\text{CHCl}_3$ )  $\nu_{\text{max}}$  1734  $\text{cm}^{-1}$ ;  $^1\text{Hmr}$  ( $\text{CDCl}_3$ ) 8.1 - 7.8 (dd,  $J = 8 \text{ Hz}$ , 2Hz, 1H), 7.5 - 7.0 (m, 3H), 4.1 (s, 3H), 4.0 (s, 2H); exact mass calcd. for  $\text{C}_{11}\text{H}_{12}\text{O}_4$  208.0735, found 208.0735.

### Attempted acyloin condensation of homophthalic acid dimethyl ester 54

To a stirred solution of 388 mg (0.017 g-atom) of Na in 100 mL anhydrous liquid  $\text{NH}_3$  (freshly distilled from Na) containing 67 mL of dry ether at  $-78^\circ\text{C}$  under  $\text{N}_2$  was added slowly a solution of 800 mg (3.84 mmol) of homophthalic acid dimethyl ester in 42 mL of dry  $\text{Et}_2\text{O}$ . At the end of the addition the blue colour had discharged and the mixture was stirred at  $-78^\circ\text{C}$  for 5 minutes more when 10 mL of  $\text{Et}_2\text{O}$  containing 5 mL of  $\text{CH}_3\text{OH}$  was added. After about 10 min., the reaction mixture was quenched using saturated  $\text{NH}_4\text{Cl}$  and  $\text{NH}_3$  was evaporated over a period of hours. The residue was taken up in  $\text{Et}_2\text{O}$  (50 mL) and washed with water. The organic layer was dried and concentrated giving 620 mg of a viscous oil. Part of this material was purified using

preparative tlc ( $C_6H_5:Et_2O$  - 65.35) giving 72 mg (47%) of crystalline solid. Recrystallization from  $H_2O$  gave 3,6-dihydro-4,5-benzo-2-pyrone 56 as a colourless solid. mp  $80-81^\circ C$  (lit.<sup>37</sup>  $81-82^\circ C$ ); IR( $CHCl_3$ )  $\nu_{max}$   $1745\text{ cm}^{-1}$ ;  $^1H_{NMR}$  ( $CDCl_3$ )  $\delta$  7.1 (s, 4H), 5.2 (s, 2H), 3.7 (s, 2H); exact mass calcd. for  $C_9H_8O_2$  148.0524, found 148.0529.

Attempted acyloin condensation of  $\gamma$ -homocinchomeric acid dimethyl ester, (38)

To a stirred solution of 125 mg (5.34 mg-atom) of Na in 100 mL anhydrous liquid  $NH_3$  (freshly distilled from Na) containing 20 mL of dry ether at  $-78^\circ C$  under  $N_2$  was added slowly a solution of 259 mg (1.2 mmol) of (38) in 7.8 mL of dry  $Et_2O$ . At the end of the addition the blue colour had discharged and the mixture was stirred at  $-78^\circ C$  for 5 minutes more when 10 mL of  $Et_2O$  containing 5 mL of  $CH_3OH$  was added. After about 10 min., the reaction mixture was quenched using saturated  $NH_4Cl$  and  $NH_3$  was evaporated over a period of hours. The residual mixture was extracted with ether (5x20 mL), drying and concentration gave 98 mg of the starting material (38). The aqueous layer was subjected to continuous extraction to give 34 mg (32%, based on recovered, (38) of 4-methyl nicotinic acid, 57. m.p.  $208^\circ C$  decomposed (lit<sup>7</sup>  $215-216^\circ C$ );  $^1H_{NMR}$  ( $D_2O$ ) 8.4-8.6 (brs, 2H), 7.8-8.0 (d,  $J=6\text{Hz}$ , 1H), 2.75 (s, 3H); mass spectrum (70 ev) m/e (rel. intensity) 137 (100%); 120 (28%), 119 (66%), 91 (40%); exact mass calcd. for  $C_7H_7NO_2$  137.0480, found

137.0476.

### 3,3-dimethyl glutaric ester (59)

Dimedone, 58, was oxidized with NaOCl giving the glutaric acid derivative.<sup>39</sup> Esterification using CH<sub>3</sub>OH-H<sub>2</sub>SO<sub>4</sub> under the usual conditions gave the diester 59 as a colourless oil.<sup>38</sup> <sup>1</sup>Hmr (CDCl<sub>3</sub>) δ 3.6 (s, 6H), 2.4 (s, 4H), 1.0 (s, 3H).

### 3,3-dimethylglutaroin (61)

4,4-dimethyl-1,2 bis(trimethylsiloxy)cyclopent-1-ene (60) was prepared using the procedure of Loudon.<sup>40</sup> <sup>1</sup>Hmr (CDCl<sub>3</sub>) δ 2.0 (s, 4H), 1.0 (s, 6H), 0.1 (s, 18H).

Hydrolysis of 60 using the procedure of Loudon<sup>40</sup> gave the α-hydroxy ketone (61) as a colourless liquid, bp 62-70°C/1.2 Torr; <sup>1</sup>Hmr δ 4.2 (m, 1H), 3.85 (brs, 1H), 2.1 (s, 2H), 2.0-1.1 (m, 2H), 1.2-1.1 (2 overlapping s, 6H).

### 1,1-dimethylcyclopentane-3,4-diol, (62)

This diol was made by the procedure of Kwart,<sup>38</sup> bp 105-110°C/1.5 Torr; <sup>1</sup>Hmr (CDCl<sub>3</sub>) δ 4.3 (m, 2H), 2.16 (m, 1H), 1.68 (m, 2H), 1.13 (2s, 6H).

### 1,2-dibromo-4,4-dimethylcyclopentane, (63)

The compound 63 was made using the procedure of Kwart.<sup>38</sup> bp 45-50°C/0.5 Torr (74-75°C/0.5 Torr<sup>38</sup>); <sup>1</sup>Hmr (CDCl<sub>3</sub>) 4.2-4.6 (m, 2H), 2.6-2.1 (m, 4H), 1.2 (2

overlapping s, 6H).

## REFERENCES

1. Nair, M.S.R.; Takeshita, H.; McMorris, T.C.; Anchel, M.  
J. Org. Chem. 1969, 34, 240.
2. Nair, M.S.R.; Anchel, M. Tetrahedron Lett. 1972, 2753.
3. Ayer, W.A.; Browne, L.M. Tetrahedron. 1981, 37, 2199.
4. Manske, R.F.H. In 'The Alkaloids' 1971, 13, 402.
5. Hanson, J.R.; Marten, T.; Nyfeler, R. J. Chem. Soc. Perkin Trans 1 1976, 876.
6. Woodward, R.B.; Hoye, T.R. J. Am. Chem. Soc. 1977, 99, 8007.
7. Wenkert, E.; Sprague, P.W.; Webb, R.L. J. Org. Chem. 1973, 38, 4305.
8. a) See Part 1 ref. 44-47.  
b) Ibid. ref. 48.
9. de Mayo, P.; Takeshita, H. Can. J. Chem. 1963, 41, 440.
10. Casals P.F.; Ferard, J.; Robert, R. Tetrahedron Lett. 3077 (1976).
11. a) Baldwin, S.W.; Gawley, R.E.; Doll, R.J.; Leung, K.H.  
J. Org. Chem. 1975, 40, 1865.  
b) Baldwin, S.W.; Gawley, R.E. Tetrahedron Lett. 1975, 3969.
12. a) Büchi, G.; Carlson, J.A.; Powell, J.E.; Titeze, L.F. J. Am. Chem. Soc. 1973, 95, 540.  
b) Partridge, J.J.; Chadha, N.K.; Uskokovic, M.R.  
J. Am. Chem. Soc. 1973, 95, 532.



13. Hikino, H.; de Mayo, P. J. Am. Chem. Soc. 1964, 86, 3582.
14. Chailand, B.D.; Hikino, H.; Kornis, G.; Lange, G.; de Mayo, P. J. Org. Chem. 1969, 34, 794.
15. Tatsuta, T.; Akimoto, K.; Kinoshita, M. J. Am. Chem. Soc. 1979, 101, 6116.
16. Birch, A.M.; Pattenden, G. J. Chem. Soc. Perkin Trans 1 1983, 1913.
17. Barker, A.J.; Pattenden, G. J. Chem. Soc. 1983, 1901.
18. Helmlinger, D.; de Mayo, P.; Nye, M.; Westfelt, L. Yeats, R.B. Tetrahedron Lett. 1970, 349.
19. Lange, G.L.; Neidert, E.E.; Orrom, W.J.; Wallace, D.J. Can. J. Chem. 1978, 56, 1628.
20. Binder, D. Monatshefte fur Chemie. 1974, 105, 196.
21. Villani, F.J.; Ellis, C.A.; Yudis, M.D.; Marton, J.B. J. Org. Chem. 1971, 36, 1709.
22. Katritzky, A.R. J. Chem. Soc. 1955, 2581.
23. Lyle, R.E.; Boyce, C.B. J. Org. Chem. 1974, 39, 3708.
24. Sobotka, W.; Beverung, W.N.; Munoz, G.G.; Sircar, J.C.; Meyers, A.I. J. Org. Chem. 1965, 30, 3667.
25. Meyers, A.I.; Beverung, W.N. J. Chem. Soc. Chem. Commun. 1968, 877.
26. Buchi, G.; Coffen, D.L.; Kocsis, K.; Sonnet, P.E.; Ziegler, F.E. J. Am. Chem. Soc. 1966, 88, 3099.
27. Caronna, T.; Fronza, G.; Minisci, F.; Porta, O. J. Chem. Soc. Perkin Trans. II 1972, 2035.

28. a) Meyers, A.I.; Gabel, R.A. J. Org. Chem. 1982, 47, 2633.  
b) Meyers, A.I.; Natale, N.R. Heterocycles 1978, 11, 133.  
c) Meyers, A.I.; Gabel, R.A. Tetrahedron Lett. 1978, 227.
29. Epsztajn, J.; Zbigniew, B.; Brzeziński, J.Z.; Józwiak, A. Tetrahedron Lett. 1980, 21, 4739.
30. Gschwend, H.W.; Rodriguez, H.R. Org. Reaction 1979, 26, 1.
31. Gribble, G.W.; Saulnier, M.G. Tetrahedron Lett. 1980, 21, 4137.
32. Ranganathan, D.; Rao, C.B.; Ranganathan, S.; Mehrotra, A.K.; Iyengar, R. J. Org. Chem. 1980, 45, 1185.
33. Akiba, K.; Iseki, Y.; Wada, M. Tetrahedron Lett. 1982, 23, 3935.
34. Morris, I.G.; Pinder, A.R. J. Chem. Soc. 1963, 1841.
35. Tomita, I.; Houston, G.; Metzler, D.E. J. Heterocyclic Chem. 1966, 3, 178.
36. a) Kirpal, A. Montash 1907, 28, 439.  
b) Giacomello, G.; Gualtieri, F.; Riccieri, F.M.; Stein, M.L. Tetrahedron Lett. 1965, 16, 1117.
37. Mann, F.G.; Stewart, H.C. J. Chem. Soc. 1954, 2819.
38. Kwart, H.; Ford, J.A. J. Org. Chem. 1959, 24, 2060.
39. Smith, W.T.; McLeod, G.I. Organic Syntheses 1963, 4, 345.

40. Ryono, D.E.; Loudon, G.M. J. Am. Chem. Soc. 1976,  
1889.

**END**

1 4 1 1 8 5

**FIN**